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(54) Title: PHOSPHORAMIDATE PRODRUGS FOR TREATMENT OF VIRAL INFECTION

(57) Abstract: The invention concerns 2'-methyl ribonucleotide phosphoramidates which are neutral prodrugs which are converted *in vivo* to 2'- methyl ribonucleotide triphosphates. These compounds are useful in the treatment of viral infection. Of particular interest are prodrugs of a methylsulfonylhydrazinyl purine 2'-methyl nucleotide triphosphate: 2'methyl- N^6-alkyl-N^6- (N-methylsulfonamide) adenosine triphosphate and its 2-amino derivative.

WO 2006/121820 A1

PHOSPHORAMIDATE PRODRUGS FOR TREATMENT OF VIRAL INFECTION

Cross Reference to Related Applications

This application claims priority to U. S. Provisional Application Ser. No. 60/678,636, filed May 5, 2005, and to U. S. Provisional Application Ser. No. 60/748,034, filed December 6, 2005, both of which are incorporated by reference herein in their entirety.

Field of the Invention

The invention relates to nucleotide drugs, which are generally useful for the treatment of viral and neoplastic diseases. The invention more specifically relates to the preparation of lipohilic nucleotide prodrugs of modified ribofuranoses, and their use for the intracellular generation of nucleotide triphosphates.

Background of the Invention

The use of nucleoside and nucleotide analogues for the treatment of HCV is accepted clinical practice. In particular, the combination of the pyrimidine nucleoside analogue ribavirin (1-β-D-ribofuranosyl-1H-1,2,4-triazole-3-carboxamide) and α-interferon constitutes the current standard therapy for HCV infection. The search for more potent nucleoside and nucleotide analogues having fewer side effects has involved not only modification of the base as in ribavirin, but also modification of the ribofuranose moiety.

A group of purine and pyrimidine nucleosides and nucleotides derived from 2'methylribofuranose are described by Sommoadossi and LaColla in WO 01/90121 and WO 01/92282 (now U.S. Patent No. 6,812,219 to Idenix). Among the compounds disclosed are those with 6-alkylamino, 6-alkylamino-8-amino, and 6-alkylamino-2-amino substitution patterns.

A further group of purine nucleotides and nucleosides for the treatment of HCV can be found in WO 02/18404 by Devos *et al.* (to F.Hoffmann-LaRoche). The nucleotides disclosed by Davos include purines having 2-amino-6-substituted amino bases and having 2',2'-difluoro or 2'-deoxy, but not 2' methyl, ribofuranose. WO 02/32920 by Stuyver and

Watanabe (to Pharmasset) makes a generic disclosure that includes but does not specifically describe 2'-methyl ribofuranose-containing nucleosides. A number of 2'-methylribonucleotides having 7-deazapurine and 7-substituted-purines is disclosed by Bhat *et al.* in U.S. Patent No. 6,777,395 (to Merck and Issis). Bhat also discloses the use of two neutral phosphate ester derivatives of nucleotides: acetyl-SATE (S-acyl-2-thioethyl) and pivaloyl-SATE, as prodrugs of the ribonucleotide analogs. SATE prodrugs are disclosed generically in U.S. Patent No. 5,770,725.

A group of 2' methylribofuranosyl purine nucleoside derivatives were disclosed by An *et al.* in WO 03/062256, which is commonly owned with the present application. The purine derivatives described by An *et al.* bears substituents at the 6-position, including hydrazino, methylhydrazino and methylsulfonylhydrazino.

Modified nucleotides and nucleosides have been widely used to treat not only HCV and other viral infections. In each case, the active drug is the nucleotide triphosphate. The compound administered to the patient is a prodrug; the active drug results from intracellular phosphorylation to yield the triphosphate. The native nucleotide is never administered to the patient because it is unstable in plasma and, being charged, does not penetrate the cell membrane. The effectiveness of modified nucleotides as anti-virals thus depends not only on the selectivity and affinity of the active drug for the viral polymerase, but also on the efficiency of the *in vivo* phosphorylation of the form that is administered.

It would be desirable to administer a monophosphorylated form of the active drug, because the phosphorylation of nucleoside analogs is usually inefficient, thereby limiting the effectivness of the drug. However, mononucleotides are unsuitable as drugs: they are unstable in plasma and, being charged at neutral pH, they are poorly transported across cell membranes. To overcome these problems, lipophilic prodrugs of known antiviral compounds have been made. (Reviewed by Zimlicka, J., *Biochem Biophy Acta* **1587**:276-86 (2002).)

Three types of nucleotide prodrugs have been prominently employed: (1) the above-noted SATE derivatives, Perigad, C., Gosselin, G., & Imbach, J-L., *Curr. Topics. Med. Chem.* **2**:15-29 (1997); (2) cyclosaligenyl derivatives, Meirer, C., *Synlett* 233-242 (1998); Balzarini, J. *et al.*, *Mol. Pharm* **58**:928-935 (2000); Balzarini, J. *et al.*, *Mol. Pharm.* **56**:1354-61 (1999); and (3) so-called "protides," (for nucleotide prodrugs) of which

phenylphosphoralaninate (PPA) derivatives are the most common. McGuigan, C., *et al.*, *J. Med. Chem.* 39:1748-53 (1996); Franchetti, P. *et al.*, *J. Med. Chem.* 37:3534-41 (1994); McGuigan, C. *et al.*, *Antiviral Res.* 17:311-321 (1992).

The PPA derivatives have been employed with several different deoxy-ribofuranosyl and dideoxy-ribofuranosyl derivatives. However, not all of the attempts have been successful. The PPA prodrug of AZT (3' azido-3'-deoxythymidine) was not successful as a prodrug for HIV treatment because the monophosphate was unstable after penetration of the cell membrane. Siddiqui A.Q., *et al.*, *Bioorg. Med. Chem. Let.* 9:2555-2560 (1999); Balzarini, J. *et al.*, *Mol. Pharm.* 56:1354-61 (1999). Likewise, the PPA derivative of 3TC (L-3' thia-2',3' dideoxycytidine) was not effective against HIV. Balzarini, J. *et al.*, *Biochem. Biophys. Res. Comun.* 225:363-69 (1996).

In contrast, the PPA derivatives of d4T (2',3' didehydro-3' deoxythymidine), d4A (2',3'-didehydro-2'3' dideoxyadenosine), and 3'-FddA (2',3'-dideoxy-3'-fluoroadenosine), were found to be superior to the parent nucleosides. Siddiqui, A.Q. *et al.*, *Bioorg.Med. Chem. Let.* 9:2555-60 (1999); McGuigan, C. *et al.*, *Bioorg. Med. Chem. Lett.* 6:2359-62 (1996); Gudmundssson, K. *et al.*, *Nucleosides, Nucleotides & Nucleic Acids* 22:1953-1961 (2001). The PPA derivative of an isodideoxyadenine was found to have *in vivo* activity whereas the related nucleoside lacks *in vivo* activity. Franchetti, P. *et al.*, *J. Med. Chem.* 37:3534-41 (1994).

While no examples of PPA-derivatized ribonucleotides are presently listed in the CAS registry file, the PPA derivative of araA (vidarabine, the 2'-β-OH isomer of adenosine), has been reported in a conference publication by Ballatore, C. *et al.*, Poster # 92, Antiviral Research 46, Absrt. # A63 (2000) (presented at the 13th International Conference on Antiviral Research, held in Baltimore, MD; reviewed by Zimlicka, J., *Biochem Biophy Acta* 1587:276-86 (2002).) This PPA derivative was reported to be inactive.

Saboulard has proposed that the activation of PPA-derivatized nucleotides takes place via a multi-step process, which is unique to protides. First, the action of a carboxyl esterase results in a free carboxylic acid, which cyclizes to displace the phenylphosphoester. The resulting cyclic anhydride is unstable, and the phosphoramidate is regenerated by hydrolysis. Finally, a phosphoramidase releases the amino acid and generates the nucleotide

monophosphate. (Saboulard, D. *et al.*, *Mol. Pharm.* 66:693-704 (1999); see also WO 00/00501.)

The PPA prodrug chemistry is described by McGuigan in U. S. Patent Nos. 6,638,919; 6,455,513; and 6,573,247; and in PCT International Publication No. WO 05/012327. Further developments are described by Uckun and Vig in WO 00/00501.

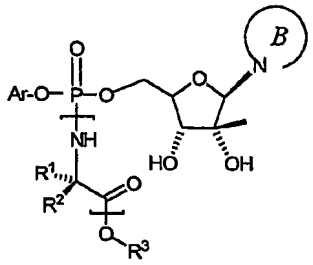
None of the McGuigan, Franchetti, and Uckun publications describes the specificity of the phosphoramidase beyond what was reported by Saboulard *et al.* Brenner *et al.* have reported studies on a ribofuranosyl phosphoramidase from yeast. They have shown activity with 5'-phosphoramidates not having an O-aryl group, *i.e.*, HOP(=O)(5'-O-adenosine)NHR. Specifically, Brenner *et al.* have shown that HOP(=O)(5'-O-adenosine)NH_2, the 5'-O-adenosine phosphoramidates of alanine methyl ester, *p*-nitroaniline, and morpholine, and the 5'-O-adenosine N^{ε} phosphoramidates of N^{α}-t-boc-lysinamide and N^{α}-acetyl-lysine methyl ester, are substrates. Bieganowski, P. *et al., J. Biol. Chem.* 277:10852-10860 (2002); Krakowiak, A. *et al., J. Biol. Chem.* 279:18711-716 (2004). The authors suggest that this phosphoramidase may be involved in the activation of PPA prodrugs.

However, none of the substrates demonstrated by Brenner *et al.* has a carboxylic acid group, as would be present in the phosphoramidase substrate in the reaction mechanism proposed by Saboulard. This, and the mixed results obtained to date with PPA prodrug forms of other nucleoside analogs, means that one cannot predict which classes of nucleosides can be successfully converted to effective prodrugs *via* the protide or PPA approach. It is presently necessary to make this determination on a case-by-case basis, which the present inventors have now done for 2'-β-methyl nucleotides.

Brief Description of the Invention

The invention is based on the unexpected result that, following entry into a cell, 2'-methyl-5'-[(O-aryl-N-alkoxycarbonylmethyl)]-phosphoramidate-ribonucleosides are rapidly and efficiently converted to the corresponding 2' methyl-nucleotide triphosphates. The invention can be practiced with any purine base, pyrimidine base, or other heteroaryl base.

Compounds of the invention have the general structure shown below:



I

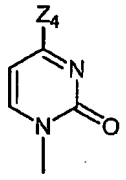
The nucleoside base (or base analogue) is indicated by *B*. The bracketed moiety is an amino acid residue. For example, when R^1 is methyl and R^2 is H, the amino acid is L-alanine. The naturally-occurring amino acids, such as L-alanine and glycine, are suitable for use in this invention. Also suitable are the synthetic amino acid dimethylglycine and synthetic amino acids where R^1 and R^2 are, independently, H or C_1 - C_5 alkyl, or where R^1 and R^2, together with the α carbon, form a ring containing 3 to 6 carbons. R^3 is any group that can be readily removed by intracellular esterases; examples of R^3 are benzyl, trifluoromethyl benzyl, methyl, or C_1-C_6 alkyl, such as methyl or isopropyl. Ar is phenyl, pyridyl, or pyrimidyl and may be unsubstituted or substituted with electron withdrawing groups. Substituents at the *para* and *ortho* positions are more effective. Suitable substituents include, but are not limited to, H, F, Cl, Br, CF_3, SO_2Me, CN and NO_2.

Compounds of the invention are useful as antiviral agents. Accordingly, the invention provides pharmaceutical compositions comprising one of more of the compounds of the invention, in combination with pharmaceutically acceptable carriers, excipients, and other additives, as are well known in the art. The pharmaceutical compositions may be adapted for oral or parenteral administration.

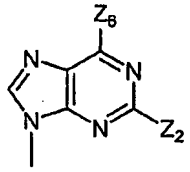
The invention also provides a method of treating a viral infection by administering to a patient in need of such treatment a pharmaceutically effective amount of one or more of the compounds or pharmaceutical compositions of the invention. The viral disease to be treated will differ, depending on which particular nucleotide the compound releases upon metabolic activation. effective amount of a compound of formula I and a pharmaceutically acceptable carrier.

Detailed Description of the Invention

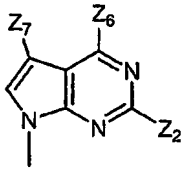
In one embodiment, this invention provides a compound of formula I, in which B is selected from the following bases B-1, B-2, and B-3,



B-1



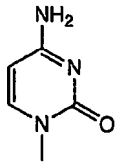
B-2

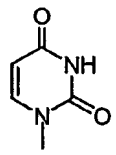


B-3

where Z_2 is H, $-NH_2$, -NHMe, or $-NMe_2$; Z_4 is $-NH_2$ or -OH; Z_6 is H, OH, OMe, OEt, SCH_3, thienyl, furyl, or $-NR_2R_3$, where R_2 is H, C_1-C_3 alkyl, or cyclopropyl, and R_3 is H or NHR_4, R_4 is H, C_1-C_4 alkyl, or SO_2R_5, and R_5 is C_1-C_4 alkyl; and Z_7 is H, halogen, or CN. All tautomeric forms are included in these definitions.

In a more specific embodiment, this invention provides a compound of formula I, in which B is B-1 and is selected from the following bases:





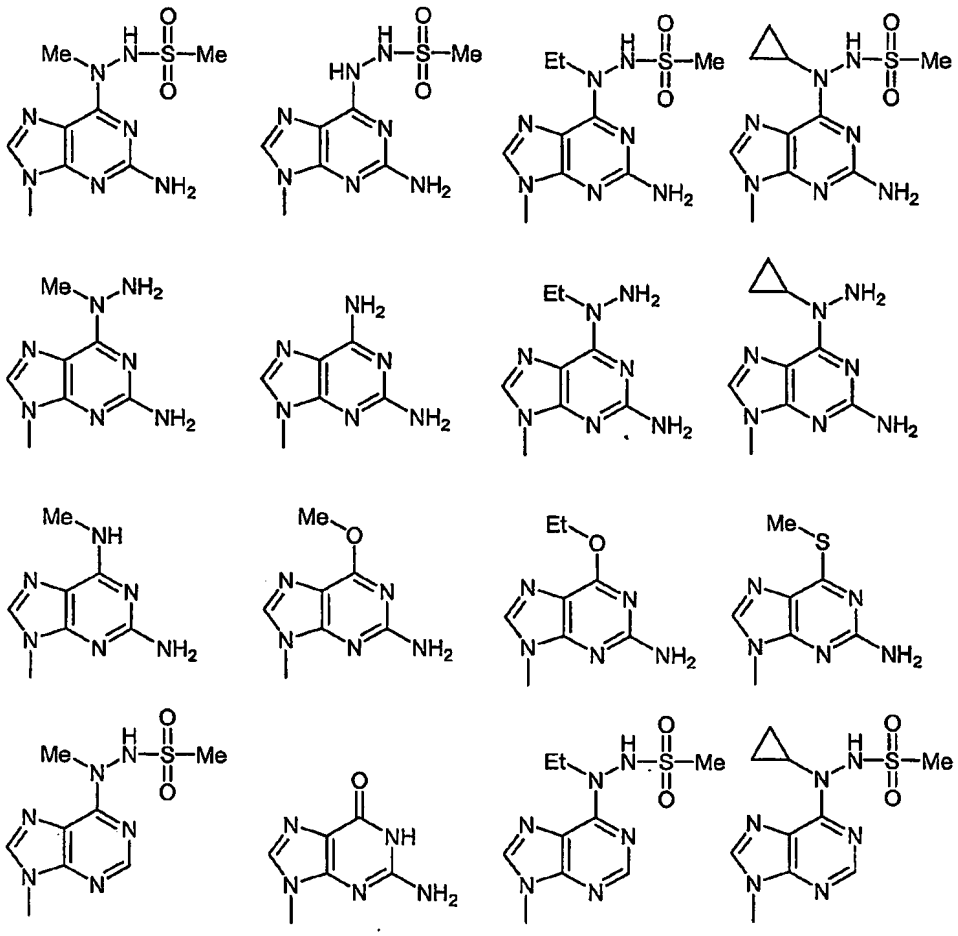
B-1-a B-1-b

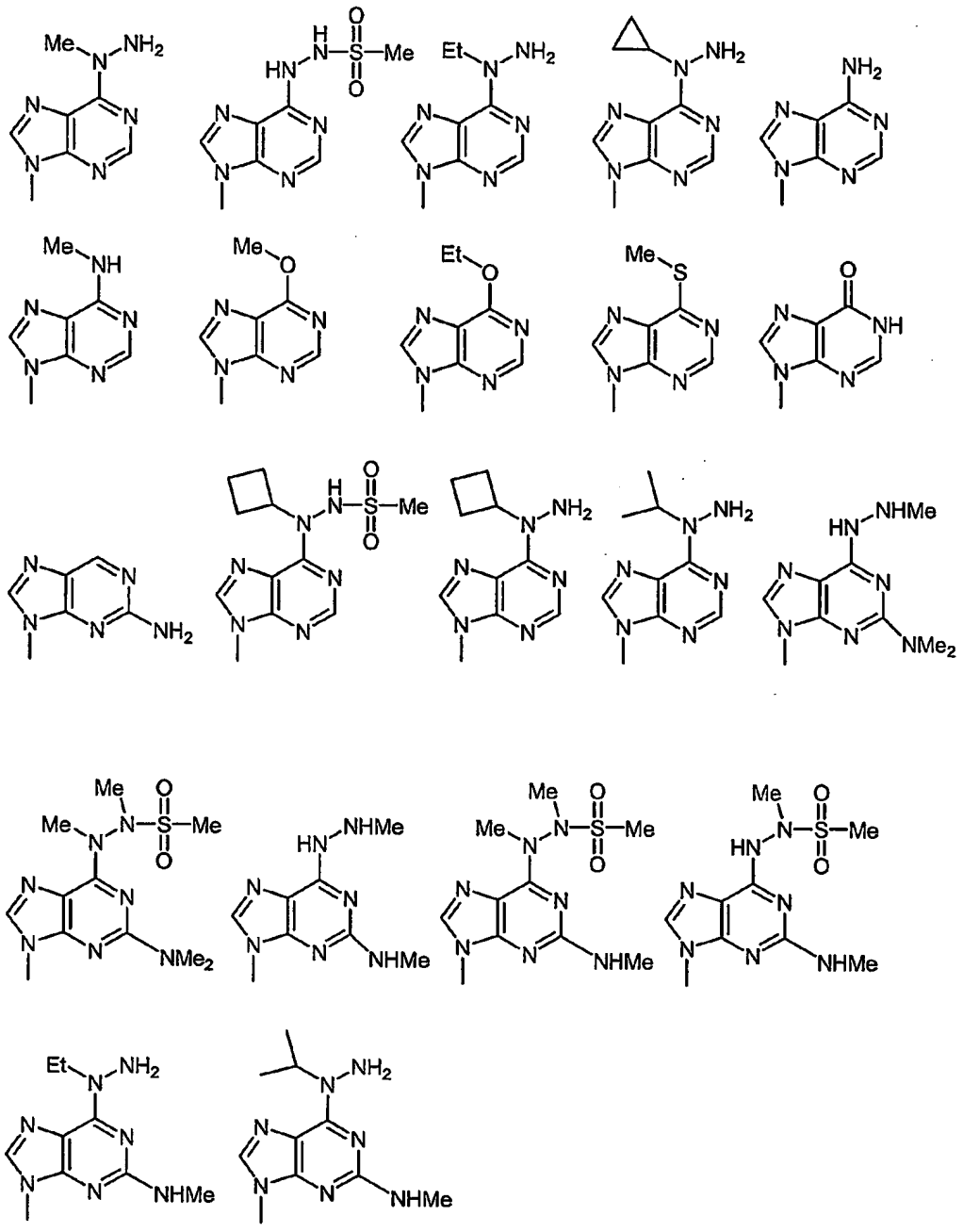
In another subgeneric embodiment, this invention provides a compound of formula I, in which B is B-2.

In a more specific embodiment, this invention provides a compound of formula I, in which B is B-2, where Z_2 is -NHMe, or $-NMe_2$.

In another more specific embodiment, this invention provides a compound of formula I, in which B is B-2, where Z_2 is H or $-NH_2$.

In another more specific embodiment, this invention provides a compound of formula I, in which B is selected from the following bases:



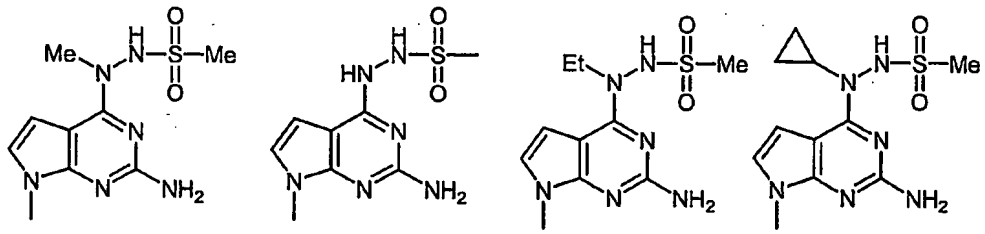


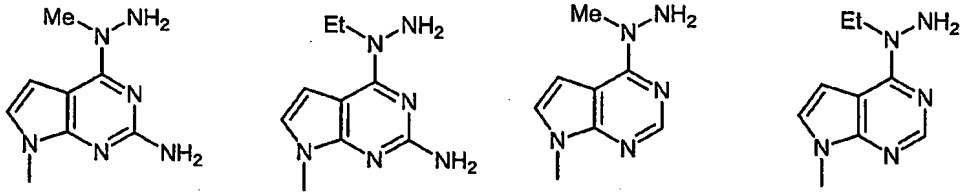
In another subgeneric embodiment, this invention provides a compound of formula I, in which B is B-3.

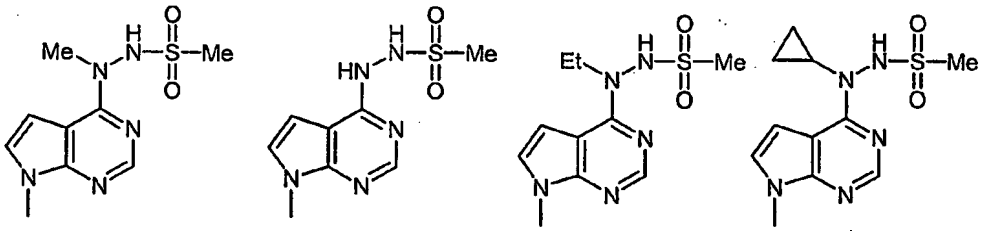
In a more specific embodiment, this invention provides a compound of formula I, in which B is B-3, where Z_2 is -NHMe, or -NMe_2.

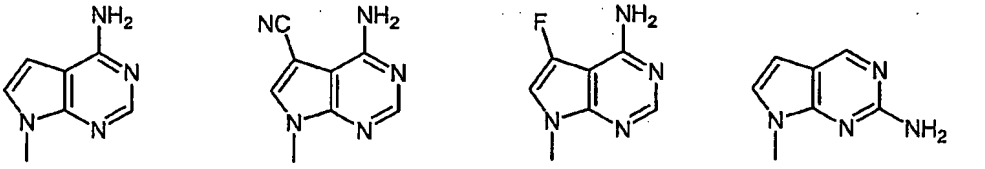
In another more specific embodiment, this invention provides a compound of formula I, in which B is B-3, where Z_2 is H or $-NH_2$.

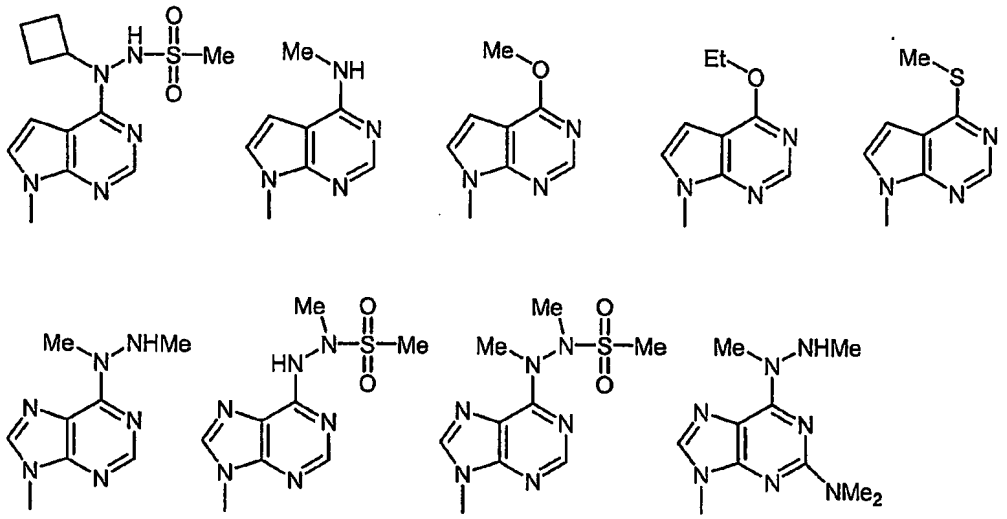
In a more specific embodiment, this invention provides a compound of formula I, in which B is B-3, selected from the following bases:

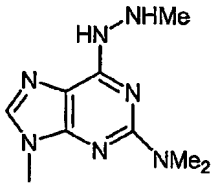




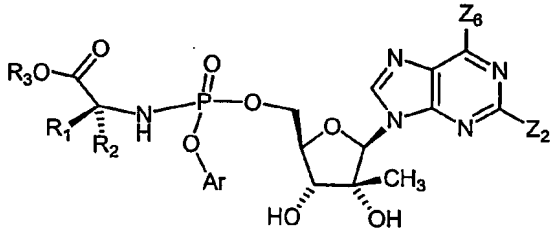








In a more specific embodiment, this invention provides or contemplates a compound of formula I-B2



I-B2

where Ar is phenyl, pyridyl, or pyrimidyl, optionally substituted with one or two groups selected independently from halo, nitro, cyano, C_1-C_3 alkyl, or C_1-C_3 alkoxy, wherein said C_1-C_3 alkyl group, and the C_1-C_3 alkyl moiety of said C_1-C_3 alkoxy group are optionally substituted with one, two, or three chlorine or fluorine atoms;

R_1 and R_2 are, independently, H, C_1-C_5 alkyl, or C_2-C_5 alkenyl, or R_1 and R_2, together with the α-carbon, form a 3- to 6- membered saturated ring;

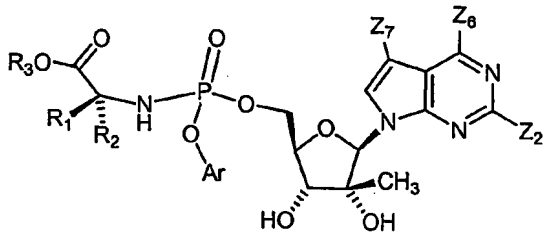
R_3 is C_1-C_6 alkyl, C_3-C_6 cycloalkyl, C_3-C_6 cycloalkyl methyl, benzyl, or phenethyl, in which the phenyl group within said benzyl or phenethyl group is optionally substituted with one or more groups selected independently from halogen, C_1-C_6 alkyl, and C_1-C_6 alkoxy, wherein said C_1-C_3 alkyl group, and the C_1-C_3 alkyl moiety of said C_1-C_3 alkoxy group are optionally substituted with one, two, or three chlorine or fluorine atoms;

Z^2 = H, NH_2, NHMe, or NMe_2; and

Z^6 = OH or NR_4R_5, where R_4 is H, C_1-C_4 alkyl, or cyclopropyl; R_5 is H or NHR_6; R_6 is H, C_1-C_4 alkyl, or SO_2R_7; and R_7 is C_1-C_4 alkyl. All tautomeric forms are included in the embodiment.

In a still more specific embodiment, the invention provides a compound of formula I-B2, where Ar is phenyl, optionally substituted as indicated above.

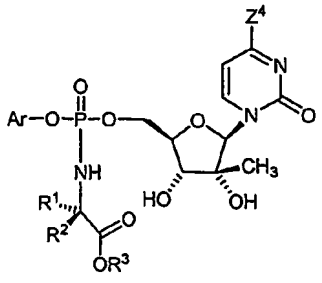
In another embodiment the invention provides a compound according to Formula I-B3



I-B3

wherein all variables are defined as above, and Z^7 is H, halogen, or CN.

In another embodiment, the invention also provides compounds of Formula I-B1



I-B1

where Ar, R_1, R_2, and R_3 are as described above and $Z^4 = NH_2$ or OH. When Z_4 is OH, this embodiment includes both the enol and keto tautomers. The enol form is depicted above.

In a more specific embodiment the invention provides or contemplates compounds of Formula I-B1, I-B-2, and I-B3, where R_1 and R_2 are, independently, H, C_1-C_5 alkyl, or C_2-C_5 alkenyl.

In a more specific embodiment the invention provides or contemplates compounds of Formula I-B1, I-B-2, and I-B3, where R_1 and R_2 are, independently, H, C_1-C_3 alkyl, or C_2-C_3 alkenyl.

In a more specific embodiment the invention provides or contemplates compounds of Formula I-B1, I-B-2, and I-B3, where R_1 and R_2 are, independently, H or methyl, or where R_1 and R_2 are $-CH_2-CH_2-$ and, together with the α carbon, form a cyclopropyl group.

In another more specific embodiment the invention provides or contemplates compounds of Formula I-B1, I-B-2, and I-B3, where R_1 and R_2 are, independently, H or methyl, or where R_1 and R_2 are $-CH_2-CH_2-CH_2-$ or $-CH_2-CH_2-CH_2--CH_2-$ and, together with the α carbon, form a cyclobutyl or cyclopentyl group.

In another more specific embodiment the invention provides or contemplates compounds of Formula I-B1, I-B2, or I-B3, where Ar is phenyl, optionally substituted with alkyl groups or with nitro, halo, or cyano groups.

In a still more specific embodiment the invention provides or contemplates compounds of Formula I-B1, I-B2, or I-B3, where Ar is phenyl, *p*-chlorophenyl or *p*-bromophenyl and R_3 is isopropyl, benzyl, *o*-methylbenzyl, or *o*-(trifluoromethyl)benzyl.

In another more specific embodiment the invention provides or contemplates compounds of Formula I-B1, I-B2, or I-B3, where R_3 is C_1-C_6 alkyl, C_3-C_6 cycloalkyl, or C_3-C_6 cycloalkyl methyl.

In another more specific embodiment the invention provides or contemplates compounds of Formula I-B1, I-B2, or I-B3, where R_3 is benzyl or phenethyl, where the phenyl group thereof is optionally substituted as described above.

In another more specific embodiment the invention provides or contemplates compounds of formula I-B2 or I-B3, where Z^6 is NR_4R_5.

In another more specific embodiment the invention provides or contemplates compounds of formula I-B2 or I-B3, where Z^6 is NR_4R_5, where R_4 is H, C_1-C_2 alkyl, or cyclopropyl; R_5 is H or NHR_6; R_6 is H, C_1-C_2 alkyl, or SO_2R_7; and R_7 is C_1-C_3 alkyl.

In another more specific embodiment the invention provides or contemplates compounds of formula I-B2 or I-B3, where Z^6 is –N(cyclopropyl)NH_2 or –N(cyclopropyl)$NHSO_2CH_3$; and Z^2 is H or NH_2.

In another more specific embodiment the invention provides or contemplates compounds of formula I-B2 or I-B3, where Z^6 is –$NMeNH_2$ or -$NMeNHSO_2CH_3$; and Z^2 is H or NH_2.

In another more specific embodiment the invention provides or contemplates compounds of formula I-B2, or I-B3, where Z^6 is NH_2 and Z^2 is H or NH_2.

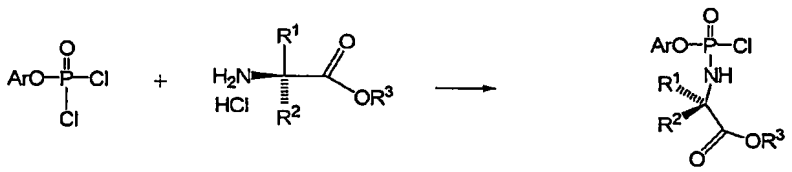
In a still more specific embodiment the invention provides or contemplates compounds of formula I-B3, where Z^6 is NH_2, Z^2 is H or NH_2, and Z^7 is F, Cl, Br, or CN.

In another still more specific embodiment the invention provides or contemplates compounds of formula I-B3, where Z^6 is NH_2, Z^2 is H or NH_2, and Z^7 is H or F.

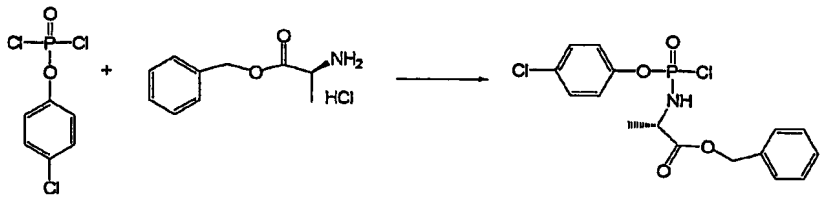
EXAMPLES

The synthesis of certain bases of the invention is described in a commonly owned application Serial No. 60/679,780, filed May 11, 2005, which is hereby incorporated by reference in its entirety. The following representative examples are provided by way of example only, and the presence or absence of specific examples does not indicate limitations on the scope of the invention.

1. General Procedure for the synthesis of phosphorochloridates



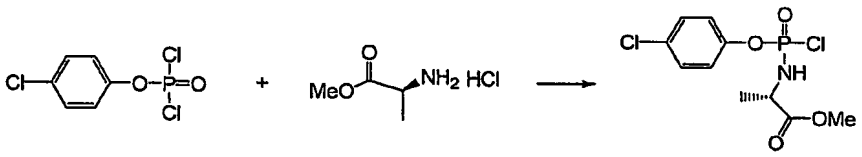
The general procedure involves reaction of an amino acid ester hydrochloride with an aryl dichlorophosphate in the presence of at least two equivalents of a suitable base. Suitable bases include, but are not limited to, imidazoles, pyridines like lutidine and DMAP, tertiary amines like triethylamine and DABCO, and substituted amidines such as DBN and DBU. Tertiary amines are particularly effective. Typically the product of each step is is preferably used directly in subsequent steps, without recrystallization or chromatography. Specific examples are provided below.



1

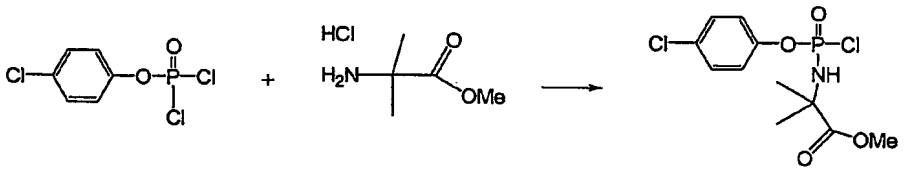
4-chlorophenyl [[(1S)-1-benzyloxycarbonylethyl]amino]phosphorochloridate (1):

Glassware and molecular sieves were dried in a 90 °C oven for 24 hours before use. To a solution of L-alanine benzyl ester hydrochloride (1g, 0.0046 mol) in anhydrous dichloromethane (3 ml) in a flask containing molecular sieves was added 4-chlorophenyldichlorophosphate (0.54 ml, 0.0033 mol). The mixture was stirred at -10 °C under argon for 10 minutes, then a solution of anhydrous triethylamine (0.92 ml, 0.0066 mol) in anhydrous dichloromethane (2 ml) was added slowly. The reaction mixture was stirred at -10 °C for 2 hours, the solid precipitated in the reaction was filtered and the filtrate was evaporated under reduced pressure. The residue was washed with ether and the filtrate collected was evaporated under reduced pressure to give **1**, which was made up as a stock solution in anhydrous tetrahydrofuran for further reaction.



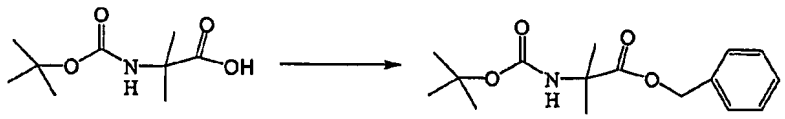
2

4-chlorophenyl [[(1S)-1-(methoxycarbonyl)ethyl]amino]phosphorochloridate (2): This compound was synthesized from L-alanine methyl ester according to the general procedure used for phosphorochloridate **1**.



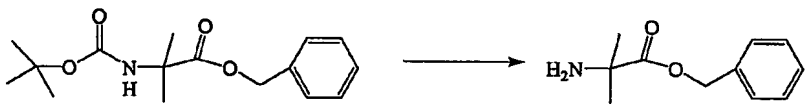
3

4-chlorophenyl [(1-methoxycarbonyl-1-methylethyl)amino]phosphorochloridate (3): This compound was synthesized from dimethylglycine methyl ester according to the general procedure used for phosphorochloridate **1**.



4

2-tert-Butoxycarbonylamino-2-methylpropionic acid benzyl ester (4): A solution of 2-*tert*-butoxycarbonylamino-2-methylpropionic acid (3 g, 0.0148 mol) in methanol (40 ml) and water (6 ml) was titrated with sat. $NaHCO_3$ to pH 9 and evaporated to dryness under reduced pressure. The salt was then stirred with benzyl chloride (2 ml, 0.0177 mol) in N,N-dimethylformamide (25 ml) at room temperature for 16 hours. The reaction mixture was evaporated under reduced pressure and the residue was partitioned between water (60 ml) and ethyl acetate (120 ml). The organic layer was dried over Na_2SO_4 and concentrated to give **4** as a clear oil (3 g, 0.01 mol, 69%); R_f= 0.5 (silica, 17% ethyl acetate in hexane).

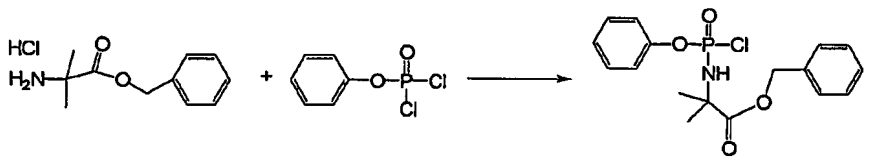


4 5

2-Amino-2-methylpropionic acid benzyl ester (5): To a solution of **4** (3 g, 0.01 mol) in anhydrous dichloromethane (15 ml) at 0 °C was added slowly trifluoroacetic acid (15 ml, 0.19 mol) with stirring at 0 °C. The mixture was stirred at 0 °C for 30 minutes and the allowed to gradually warm to room temperature over 4 hours. The reaction mixture was evaporated under reduced pressure and was extracted with ethyl acetate and washed with 3x15 ml water. The organic layer was dried over Na_2SO_4 and concentrated to give **5** (1.9 g, 100%) as a yellow oil; R_f= 0.8 (silica, 17% methanol in chloroform); ^{1}H NMR (300MHz, d6-DMSO) δ 8.48 (s, 2H), 7.40- 7.34 (m, 5H), 5.23 (s, 2H), 1.46 (s, 6H).

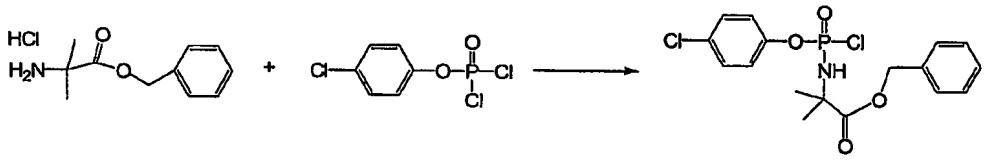
2-Amino-2-methylpropionic acid benzyl ester hydrochloride (6): A 1M solution of hydrochloric acid in diethyl ether (25 ml, 0.025 mol) was added to 2-amino-2-methylpropionic acid benzyl ester (**5**) (1.9 g, 0.01 mol) at 0 °C, and the mixture was stirred for 16 hours. The precipitate was collected and washed with diethyl ether to give pure (**6**) (1.46 g, 0.006 mol,

60%) as a white solid; ^{1}H NMR (300MHz, d6-DMSO) δ 8.62 (s, 3H), 7.40- 7.35 (m, 5H), 5.23 (s, 2H), 1.48 (s, 6H).



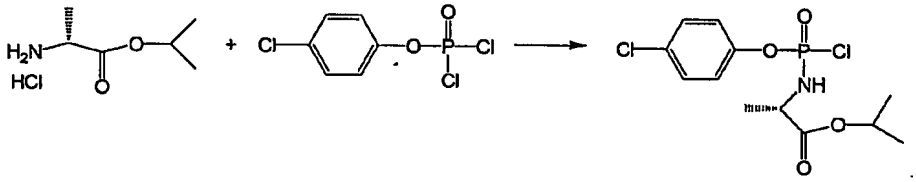
6 7

Phenyl [(1-benzyloxycarbonyl-1-methylethyl)amino]phosphorochloridate (7): This was synthesized from the amino acid ester hydrochloride **6** according to the general procedure (1).



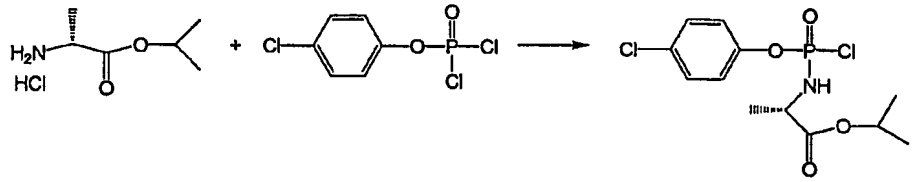
6 8

4-chlorophenyl [(1-benzyloxycarbonyl-1-methylethyl)amino]phosphorochloridate (8): This was also synthesized from the amino acid ester hydrochloride **6** according to the general procedure (1).



9

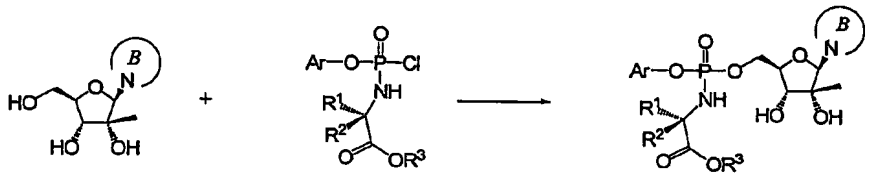
4-Chlorophenyl [[(1S)-1-(1-methylethoxycarbonyl)ethyl]amino]phosphorochloridate (9): To a solution of L-alanine isopropyl ester hydrochloride (1 g, 0.006 mol) in anhydrous dichloro-methane (5 ml) was added 4-chlorophenyl dichlorophosphate (0.7 ml, 0.004 mol) at -20 °C. A solution of anhydrous triethylamine (1.12 ml, 0.008 mol) in anhydrous dichloromethane (1 ml) was added, and the mixture was stirred at -20 °C for 30 minutes. The precipitated was filtered off and the solution was evaporated under reduced pressure. The residue was washed with ether and the filtrate was collected evaporated under reduced pressure to give the phosphorochloridate **9** which was made up as a stock of solution in anhydrous tetrahydrofuran for further reaction.



10

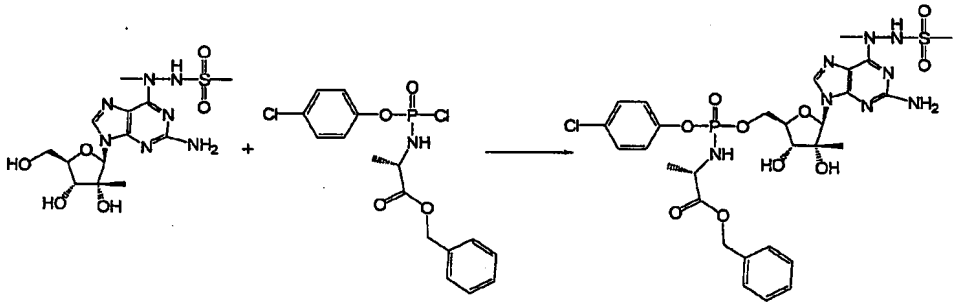
Phenyl [[(1S)-1-(1-methylethoxycarbonyl)ethyl]amino]phosphorochloridate (10): This compound was prepared according to the general procedure (1) in the same manner as compound **9**.

2. General Procedure for the synthesis of nucleoside 5'-O-phosphoramidates



The general procedure involves reaction of a nucleoside or a 7-deazanucleoside with a free 5' OH with an amino acid derivative of a phosphorochloridate, in the presence of a suitable base. Suitable bases include, but are not limited to, imidazoles, pyridines such as lutidine and DMAP, tertiary amines such as triethylamine and DABCO, and substituted amidines such as DBN and DBU. The product may be isolated by recrystallization and/or chromatography. Specific examples are provided below.

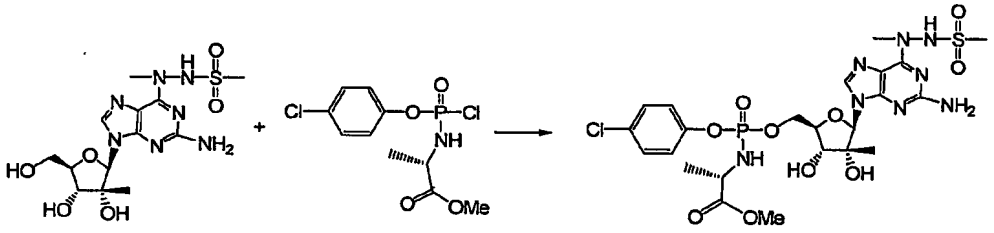
Due to the chirality of the phosphorous atom, all nucleoside phosphoramidates described herein are obtained and tested as mixtures of enantiomers and diastereomers. The present invention also encompasses the individual pure stereoisomers, which may be obtained by high-performance liquid chromatography of the final products, or by the use of enantiomerically or diastereomerically pure phosphorochloridates, as is known in the art.



1 IV

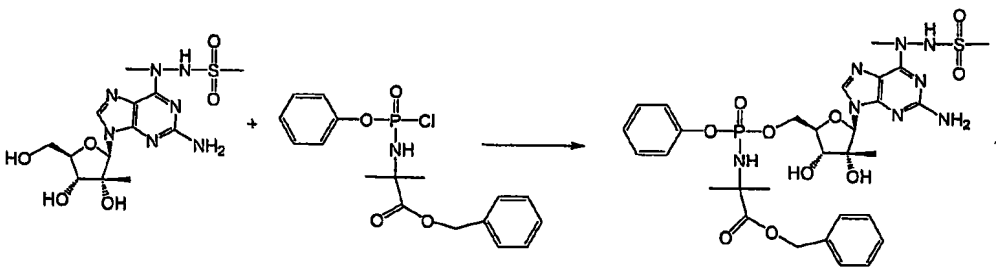
9-[5'-*O*-[[[(1S)-1-(benzyloxycarbonyl)ethylamino]-4-chlorophenoxyphosphinyl]-2'β-methyl-β-D-arabinofuranosyl]adenine (IV): A solution of 2-amino-N^6-methyl-N^6-methylsulfonamido-9-(2'β-methyl-β-D-ribofuranosyl)adenine (0.1 g, 0.248 mmol) in anhydrous dichloromethane (2 ml) at -10°C under argon was added slowly a solution of 4-chlorophenyl [[[(1S)-1-benzyloxycarbonyl]ethyl]amino]phosphorochloridate (1) (1.85 ml, 0.744 mmol) and 1-methylimidazole (0.08 ml, 0.992 mmol) in anhydrous dichloromethane (1 ml). The reaction mixture was stirred at -10 °C to -20 °C for 2 hours then gradually stirred at room temperature for 20 hours.

The mixture was diluted with dichloromethane and washed with 2 x 1 ml 1N HCl, 2 x 1 ml sat. $NaHCO_3$, and 2 x 5 ml brine, then back-extracted with dichloromethane. The combined organic layers were dried over Na_2SO_4 and evaporated under reduced pressure, and the residue was purified by silica gel chromatography with a gradient of 8% methanol in chloroform to afford the product as a yellow paste (68.4 mg, 0.062 mmol, 25%); R_f= 0.7 (silica, 17% methanol in chloroform); ^{1}H NMR (300MHz, d6-DMSO) δ 7.91 (s, 1H), 7.37- 7.16 (m, 9H), 6.35 (s, 2H), 5.86 (s, 1H), 5.49 (s, 1H), 5.27 (s, 1H), 5.06 (s, 2H), 4.35- 3.86 (m, 4H), 3.67 (s, 3H), 3.15 (d, 1H, *J*= 3.6Hz), 3.00 (s, 3H), 1.22 (d, 3H, *J*= 7.2Hz), 0.81 (s, 3H).



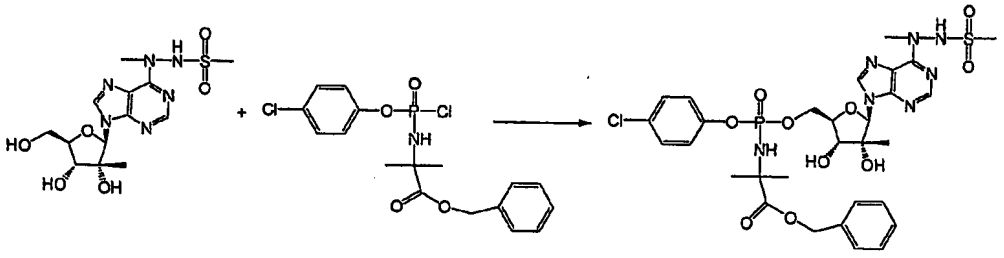
2 V

9-[5'-*O*-[[(1S)-1-(methoxycarbonyl)ethylamino]-4-chlorophenoxyphosphinyl]-2'β-methyl-β-D-arabinofuranosyl]adenine (V): This compound was synthesized according to the general procedure (2), using the same process as for the preparation of **IV** above but with the phosphorochloridate **2**. It was isolated as a yellow paste (17.5 mg, 0.026 mmol, 10%); R_f= 0.7 (silica, 17% methanol in chloroform); ^{1}H NMR (300MHz, d6-DMSO) δ 7.92 (s, 1H), 7.53 (s, 1H), 7.42- 7.39 (m, 1H), 7.24- 7.19 (m, 1H), 7.08 (s, 1H), 6.85 (s, 1H), 6.35 (s, 2H), 5.85 (s, 1H), 5.47- 5.25 (m, 2H), 4.38- 4.03 (m, 4H), 3.67 (s, 3H), 3.62 (s, 1H), 3.53 (d, 3H, *J*= 1.8Hz), 3.00 (s, 3H), 1.22- 1.18 (m, 3H), 0.82 (s, 3H).



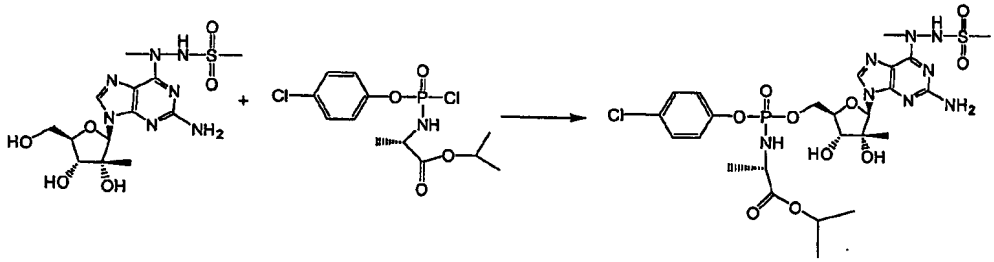
7 VI

9-[5'-*O*-[[(1-methoxycarbonyl-1-methylethyl]amino] phenoxyphosphinyl]-2'β-methyl-β-D-arabinofuranosyl]adenine (VI): This compound was synthesized according to the general procedure (2). The product was obtained as a yellow paste (6.4 mg, 0.009 mmol, 4%); R_f= 0.6 (silica, 17% methanol in chloroform); ^{1}H NMR (300MHz, d6-DMSO) δ 8.75 (s, 2H), 7.98-7.30 (m, 10H), 6.35 (s, 2H), 5.87 (s, 1H), 5.46- 5.23 (m, 2H), 5.02 (s, 2H), 4.72- 4.03 (m, 4H), 3.80 (s, 3H), 2.99 (s, 3H), 1.46- 1.13 (m, 6H), 0.87 (s, 3H).



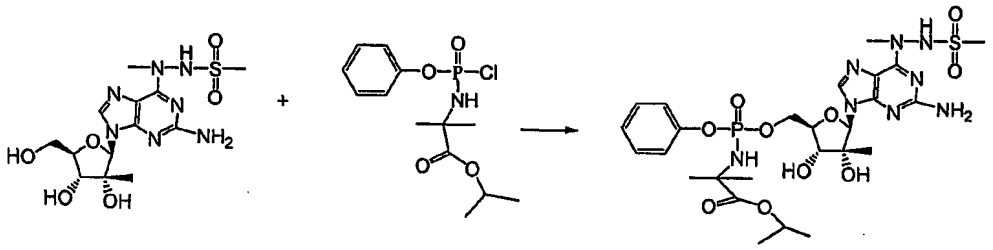
8 VII

9-[5'-*O*-[[(1-methoxycarbonyl-1-methylethyl)amino]-4-chlorophenoxyphosphinyl]-2'β-methyl-β-D-arabinofuranosyl]adenine (VII): This was synthesized according to the general procedure (2). The product was isolated as a brown paste (9.9 mg, 0.01 mmol, 4%); R_f= 0.6 (silica, 17% methanol in chloroform); ^{1}H NMR (300MHz, CD_3OD) δ 8.42 (s, 1H), 8.36 (s, 1H), 7.41- 7.21 (m, 9H), 6.23 (s, 1H), 5.11 (s, 2H), 4.62- 3.99 (m, 4H), 3.86 (s, 3H), 2.98 (s, 3H), 1.29 (s, 6H), 1.05 (s, 3H).



9 VIII

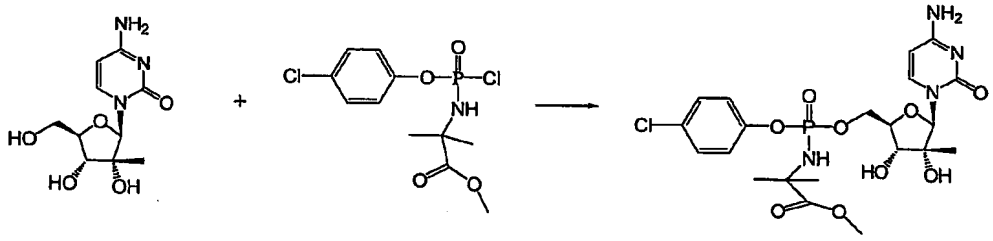
9-[5'-*O*-[[[1-(1-methylethoxycarbonyl)-1-methylethyl]amino]-4-chlorophenoxyphosphinyl]-2'β-methyl-β-D-arabinofuranosyl]adenine (VIII): This was synthesized according to the general procedure (2). The product was obtained as a yellow paste (12.3 mg, 0.017 mmol, 7%); R_f= 0.7 (silica, 17% methanol in chloroform); ^{1}H NMR (300MHz, d6-DMSO) δ 7.92 (s, 1H), 7.40 (d, 2H, *J*= 8.7Hz), 7.23 (d, 2H, 5.4Hz), 6.34 (s, 2H), 5.85 (s, 1H), 5.45- 5.24 (m, 2H), 4.82- 4.76 (m, 1H), 4.34- 4.03 (m, 5H), 3.67 (s, 3H), 3.00 (s, 3H), 1.21- 1.06 (m, (H), 0.82 (s, 3H).



10 IX

9-[5'-*O*-[[[1-(1-methylethoxycarbonyl)-1-methylethyl]amino]-4-chlorophenoxyphosphinyl]-2'β-methyl-β-D-arabinofuranosyl]adenine (IX): This compound was synthesized according to the general procedure (2) by the same method as compound **VII**. It was isolated as a yellow paste (16.6 mg, 0.024 mmol, 12%); R_f= 0.7 (silica, 17% methanol in chloroform); ^{1}H NMR (300MHz, CD_3OD) δ 7.96 (s, 1H), 7.33- 7.17 (m, 5H), 5.97 (s, 1H), 4.54- 4.15 (m, 5H), 3.77 (s, 3H), 2.95 (s, 3H), 1.43 (d, 6H, *J*= 10.5Hz), 1.22- 1.19 (m, 6H), 0.97 (s, 3H).

Derivatives of B-1:



[5-*O*-(4-chlorophenyl methoxydimethylglycinylphosphate)-(2-C-methyl-β-D-ribofuranosyl)cytosine] A solution of (2-C-methyl-β-D-ribofuranosyl)cytosine (0.066g, 0.257mmol) in anhydrous dichloromethane (1.5ml) at -10°C under argon was added slowly a solution of 4-Chlorophenyl methoxydimethylglycinylphosphorochloridate (1.2ml, 0.769mmol) and 1-methylimidazole (0.12ml, 1.54mmol) in anhydrous dichloromethane (0.5ml). The

reaction mixture was stirred at -10°C/-20°C for 2 hours then gradually stirred at room temperature for 8 hours. The mixture was evaporated under reduced pressure, and the crude was purified by silica gel chromatography in a gradient of 8% methanol in chloroform to afford the product as a yellow paste (28mg, 0.05mmol, 19%)

5

BIOLOGICAL ACTIVITY

The anti-HCV activities of the exemplary compounds were tested in two biological assays: a cell-based HCV replicon assay and a cytotoxicity assay.

1. HCV Replicon Assay

A human hepatoma cell line (Huh-7) containing replicating HCV Con1 subgenomic replicon with a luciferase reporter gene (luc-ubi-neo) was used to evaluate anti-HCV activity of the compounds. In this assay, the level of luciferase signal correlates directly with the viral RNA replication. The HCV replicon-reporter cell line (NK/luc-ubi-neo) was cultured in DMEM medium supplemented with 10 % fetal bovine serum and 0.5 mg/ml Geneticin (G418). Cells were maintained in a subconfluent state to ensure high levels of HCV replicon RNA synthesis.

To evaluate the antiviral activity of compounds, serial dilutions were prepared with concentrations ranging from 0.14 to 300 μM. Diluted compounds were transferred to a 96-well plate followed by the addition of replicon cells (6000 cells per well). Cells were incubated with the compounds for 48 hours after which luciferase activity was measured. Reduction of luciferase signal reflected the decrease of HCV replicon RNA in the treated cells and used to determine the EC_{50} value (concentration which yielded a 50 % reduction in luciferase activity).

2. Cytotoxicity Assay

A Huh-7 cell line carrying a luciferase reporter gene (driven by a HIV LTR promoter) stably integrated into the chromosome was used to analyze the cytotoxic effect of the selected compounds. This cell line (LTR-luc) was maintained in DMEM medium with 10 % FBS. Design of the cytotoxicity assay was similar to that of the HCV replicon assay. Reduction of luciferase activity in the treated cells correlated with the cytotoxic effect of the test compound and was used to calculate the CC_{50} value (concentration that inhibited cell growth by 50%).

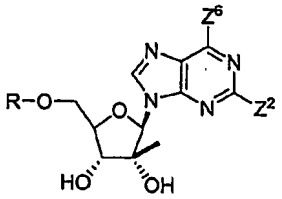
The biological activities and cytotoxicity of the selected compounds are summarized in Tables 1 and 2.

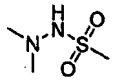
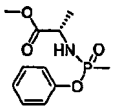
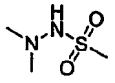
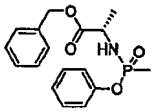
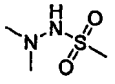
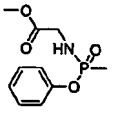
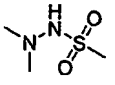
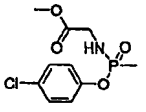
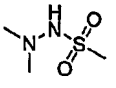
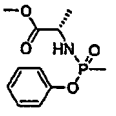
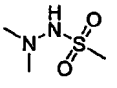
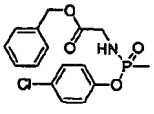
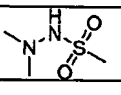
BIOLOGICAL ACTIVITIES OF SELECTED COMPOUNDS

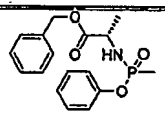
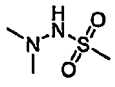
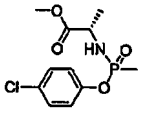
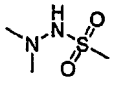
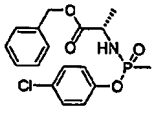
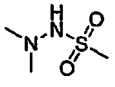
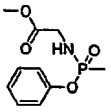
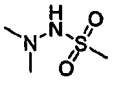
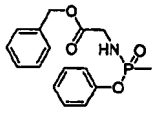
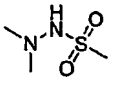
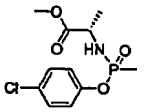
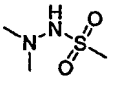
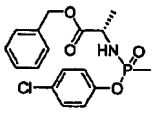
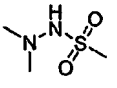
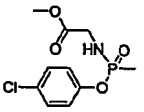
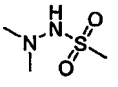
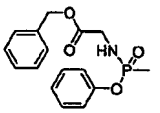
Legend: EC_{50}: A (<0.25 μM), B (0.25 to 1.0 μM) and C (1.0 to 50 μM)

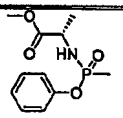
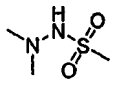
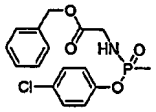
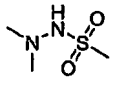
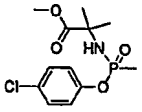
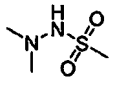
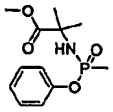
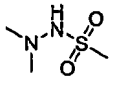
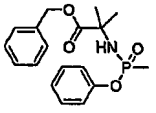
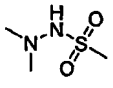
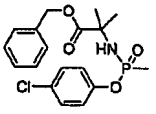
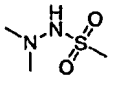
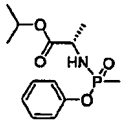
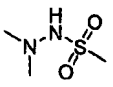
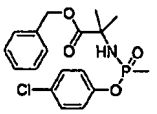
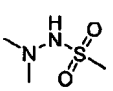
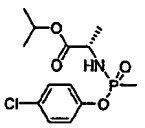
CC_{50}: A (>300 μM), B (50 to 300 μM) and C (<50 μM)

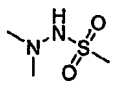
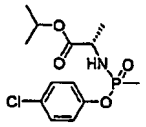
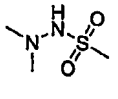
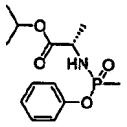
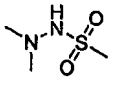
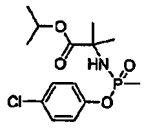
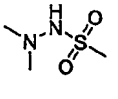
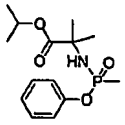
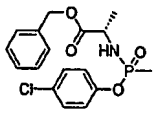
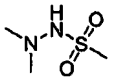
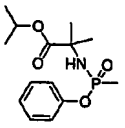
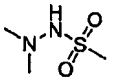
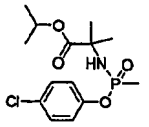
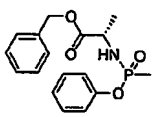
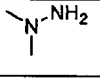
TABLE 1-ACTIVITY OF COMPOUNDS OF FORMULA I-B2

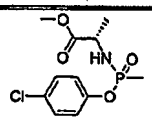
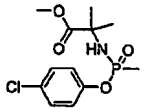
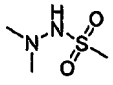
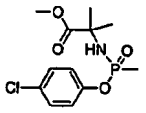
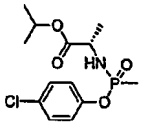
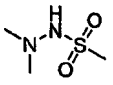
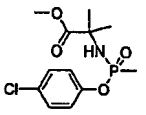
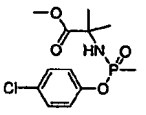
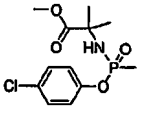
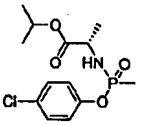


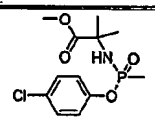
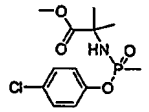
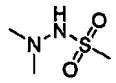
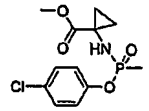
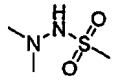
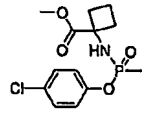
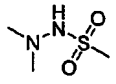
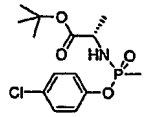
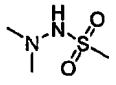
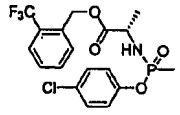
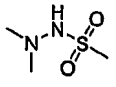
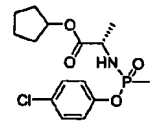
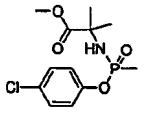
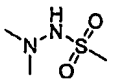
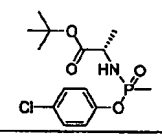
Cpd ID	Z^2	Z^6	R	EC_{50} (μM)	CC_{50} (μM)
1	H			C	A
2	H			C	A
3	H			D	A
4	H			C	A
5	NH_2			C	A
6	H			C	A
7	NH_2			C	A

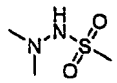
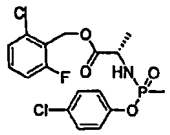
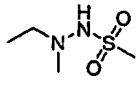
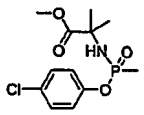
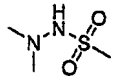
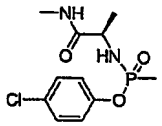
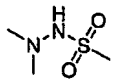
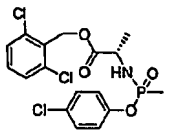
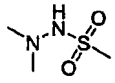
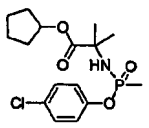
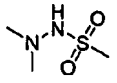
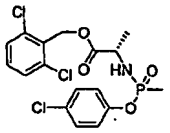
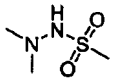
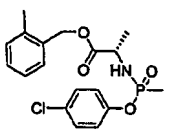
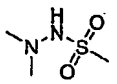
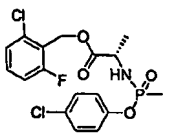
Cpd ID	Z^2	Z^6	R	EC_{50} (μM)	CC_{50} (μM)
					
8	H			C	A
9	H			B	B
10	NH_2			C	A
11	NH_2			C	B
12	NH_2			B	A
13	NH_2			A	B
14	NH_2			C	A
15	H			C	A
16	NH_2			B	A

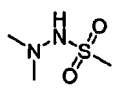
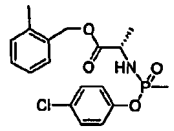
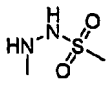
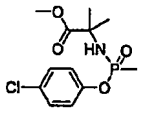
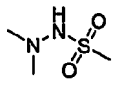
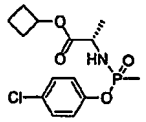
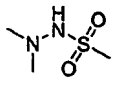
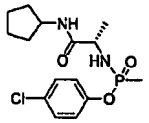
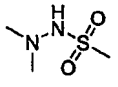
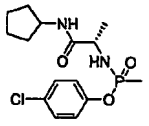
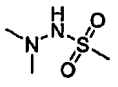
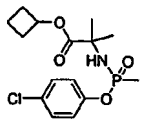
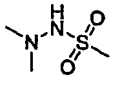
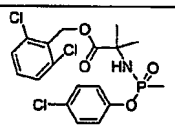
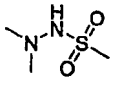
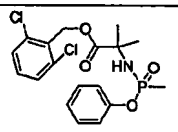
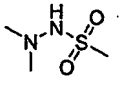
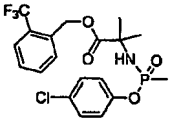
Cpd ID	Z^2	Z^6	R	EC_{50} (μM)	CC_{50} (μM)
					
17	NH_2			B	B
18	NH_2			A	B
19	NH_2			B	B
20	NH_2			C	B
21	H			C	A
22	H			C	B
23	NH_2			B	B
24	H			C	B

Cpd ID	Z^2	Z^6	R	EC_{50} (μM)	CC_{50} (μM)
25	NH_2			B	B
26	NH_2			B	A
27	NH_2			B	B
28	NH_2			B	B
29	NH_2			A	C
30	H			B	>300
31	H			C	B
32	NH_2			A	A
33	H			A	A

Cpd ID	Z^2	Z^6	R	EC_{50} (μM)	CC_{50} (μM)
					
34	NH_2			A	B
35	H			B	B
35	H			A	B
37	H			A	A
38	NH_2	OMe		A	B
39	H	NHMe		A	B
40	NH_2			A	C
41	H	NH_2		B	B

Cpd ID	Z^2	Z^6	R	EC_{50} (μM)	CC_{50} (μM)
					
42	NH_2	NH_2		C	B
43	NH_2			C	B
44	NH_2			B	B
45	NH_2			B	B
46	NH_2			A	B
47	NH_2			A	B
48	NHMe	O		A	B
49	NH_2			C	C

Cpd ID	Z^2	Z^6	R	EC_{50} (μM)	CC_{50} (μM)
50	H			A	B
51	NH_2			C	C
52	H			C	B
53	NH_2			A	C
54	NH_2			A	B
55	H			B	C
56	NH_2			A	B
57	NH_2			A	B

Cpd ID	Z^2	Z^6	R	EC_{50} (μM)	CC_{50} (μM)
58	H			B	B
59	NH_2			C	B
60	NH_2			B	B
61	H			C	B
62	NH_2			C	B
63	NH_2			B	B
64	NH_2			B	B
65	H			C	B
66	NH_2			A	B

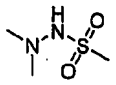
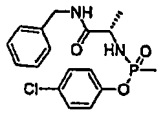
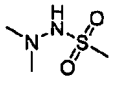
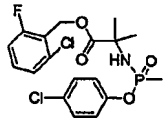
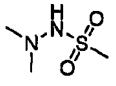
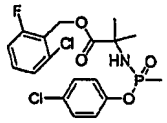
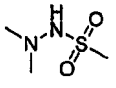
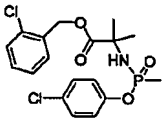
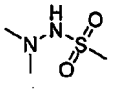
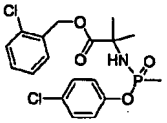
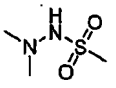
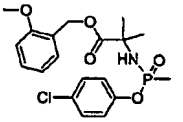
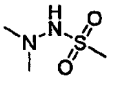
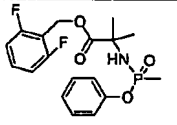
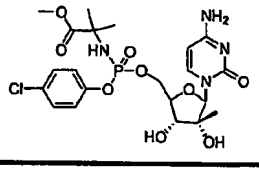
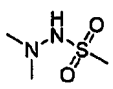
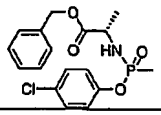
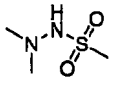
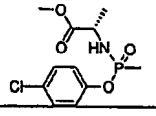
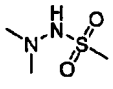
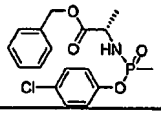
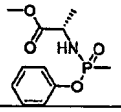
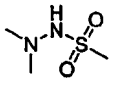
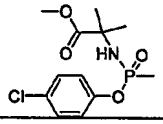
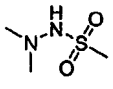
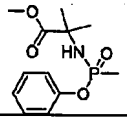
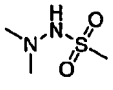
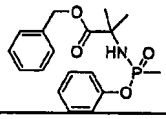
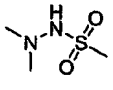
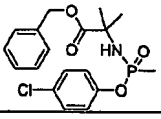
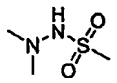
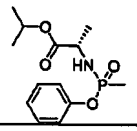
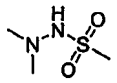
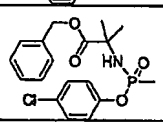
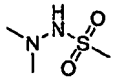
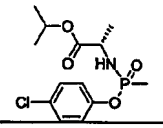
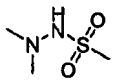
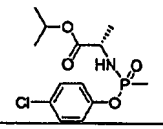
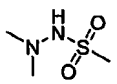
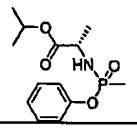
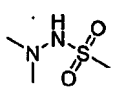
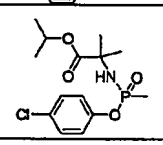
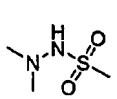
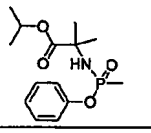
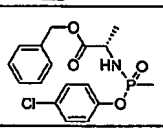
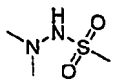
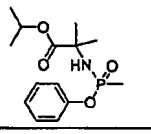
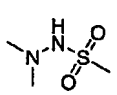
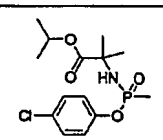
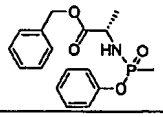
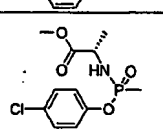
Cpd ID	Z^2	Z^6	R	EC_{50} (μM)	CC_{50} (μM)
67	NH_2			C	B
68	NH_2			A	C
69	NH_2			A	B
70	NH_2			A	B
71	NH_2			A	B
72	NH_2			A	B
73	H			A	B

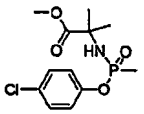
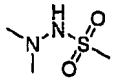
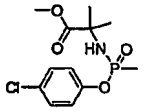
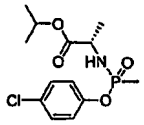
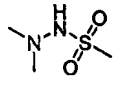
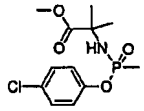
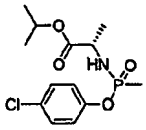
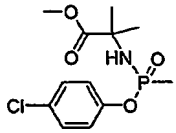
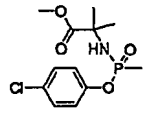
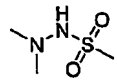
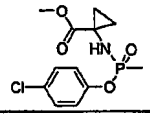
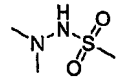
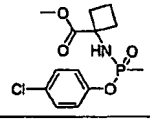
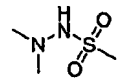
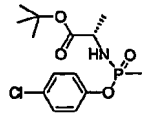
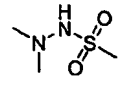
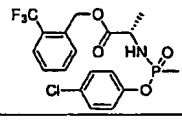
Table 2 ACTIVITY OF COMPOUNDS OF FORMULA I-B1

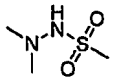
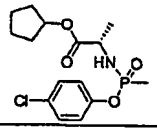
COMPOUND	EC_{50} (μM)	CC_{50} (μM)
	C	B

5

Cpd ID	R_1	R_2	R_3	EC_{50} (μM)	CC_{50} (μM)
1	H			B	C
2	NH_2			B	A
3	NH_2			A	B
4	NH_2			B	A
5	NH_2			B	A
6	NH_2			B	B
7	NH_2			C	B
8	H			D	B

9	H			D	B
10	NH_2			C	B
11	H			C	B
12	NH_2			B	B
13	NH_2			B	B
14	NH_2			B	B
15	NH_2			A	C
16	NH_2			C	D
17	H			A	B
18	H			B	B
19	NH_2			B	B
20	H			B	B

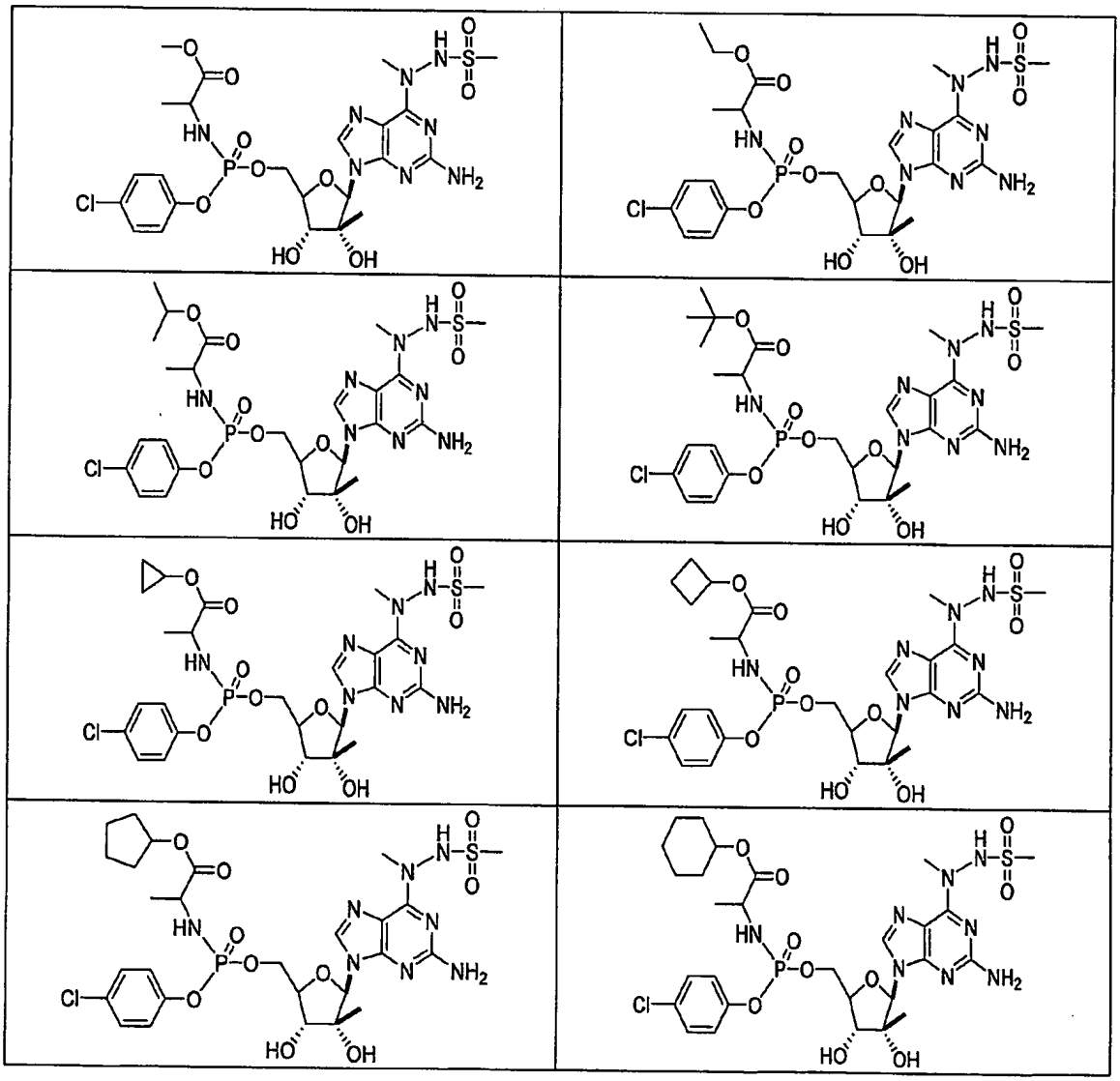
21	NH_2			A	B
22	H			A	B
23	H			A	B
24	H			A	B
25	NH_2			A	D
26	H	NH_2		B	C
27	NH_2	NH_2		C	C
28	NH_2			C	C
29	NH_2			A	C
30	NH_2			A	C
31	NH_2			A	B

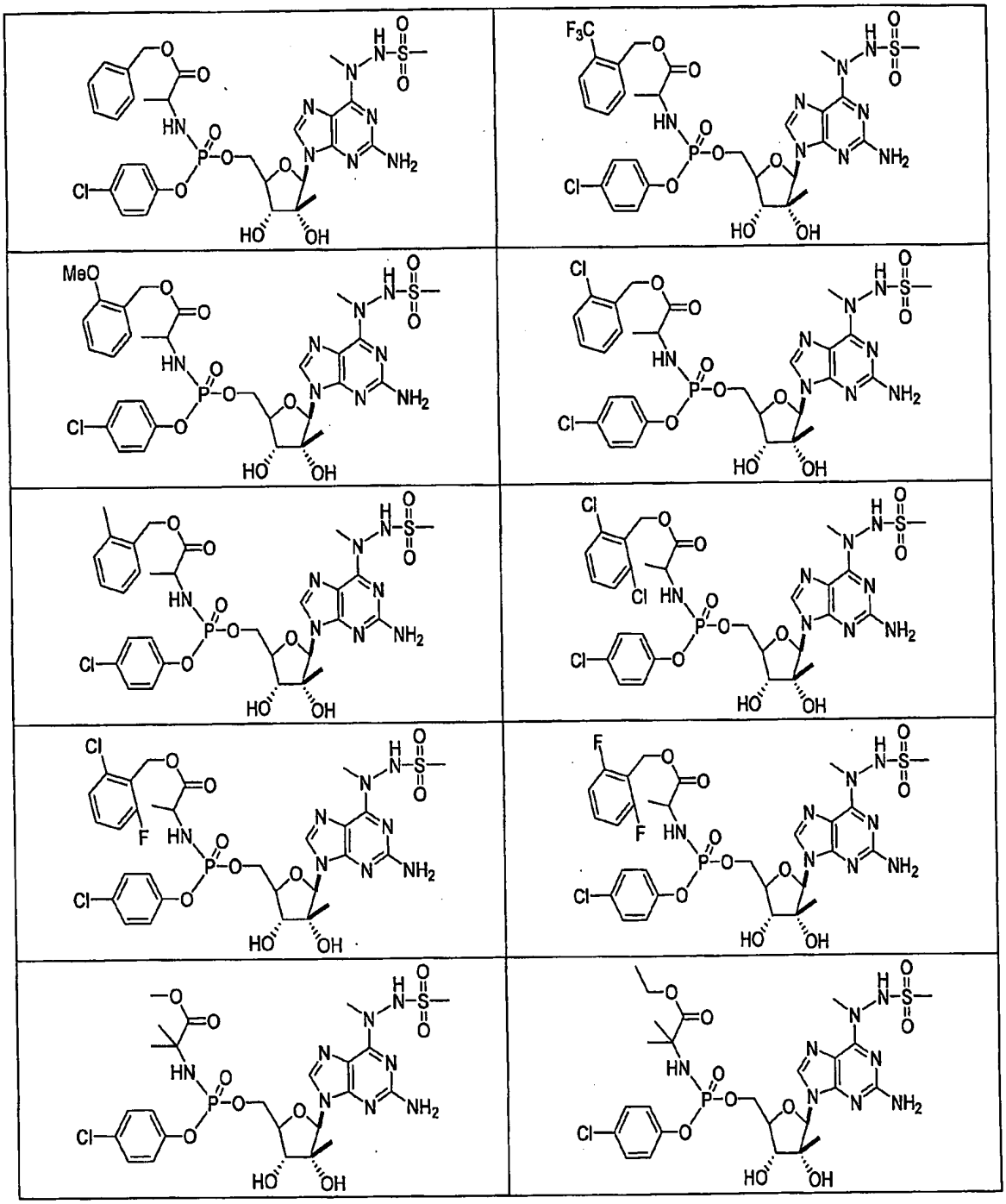
32	NH_2			A	C

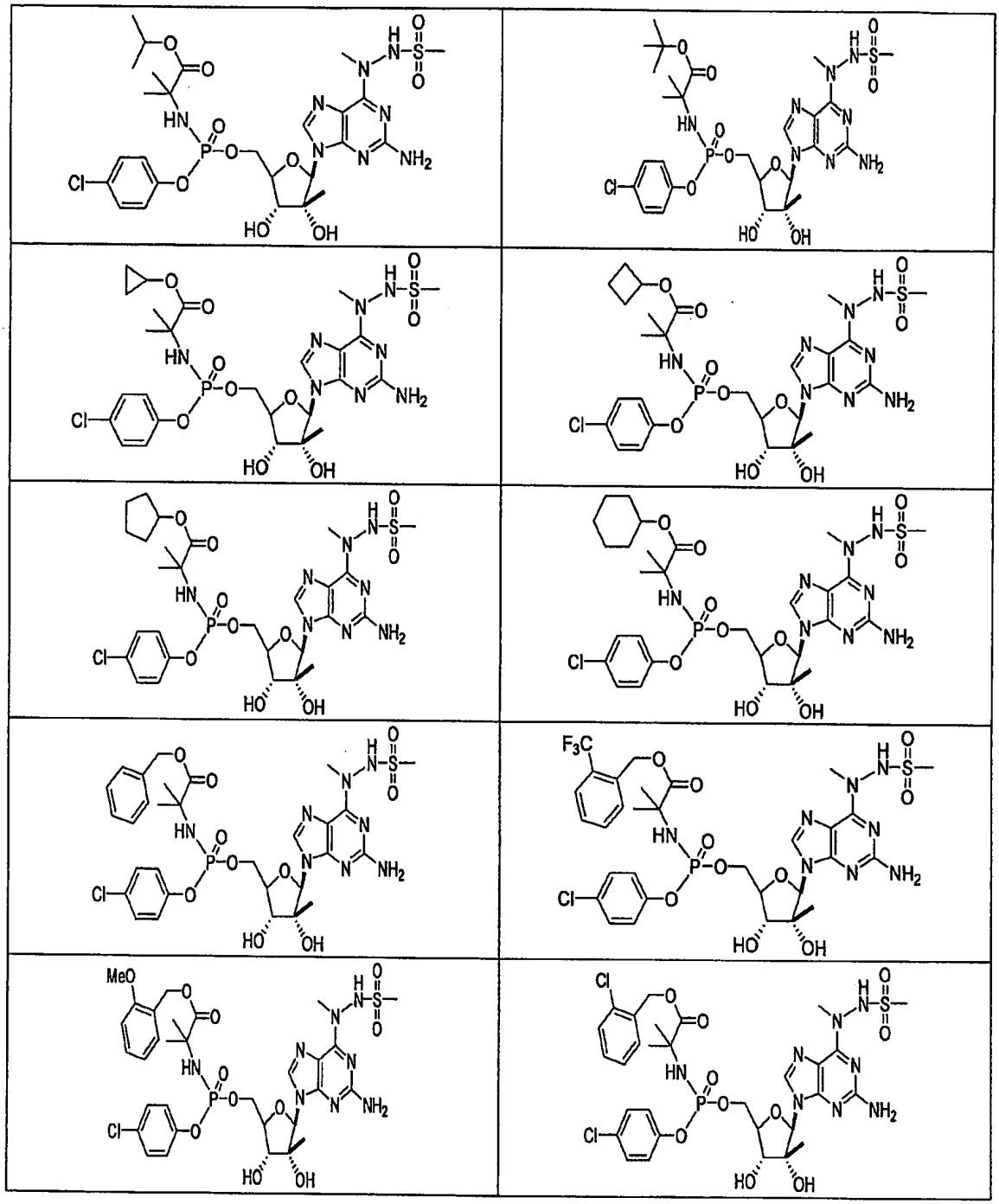
The following table shows contemplated compounds of this invention.

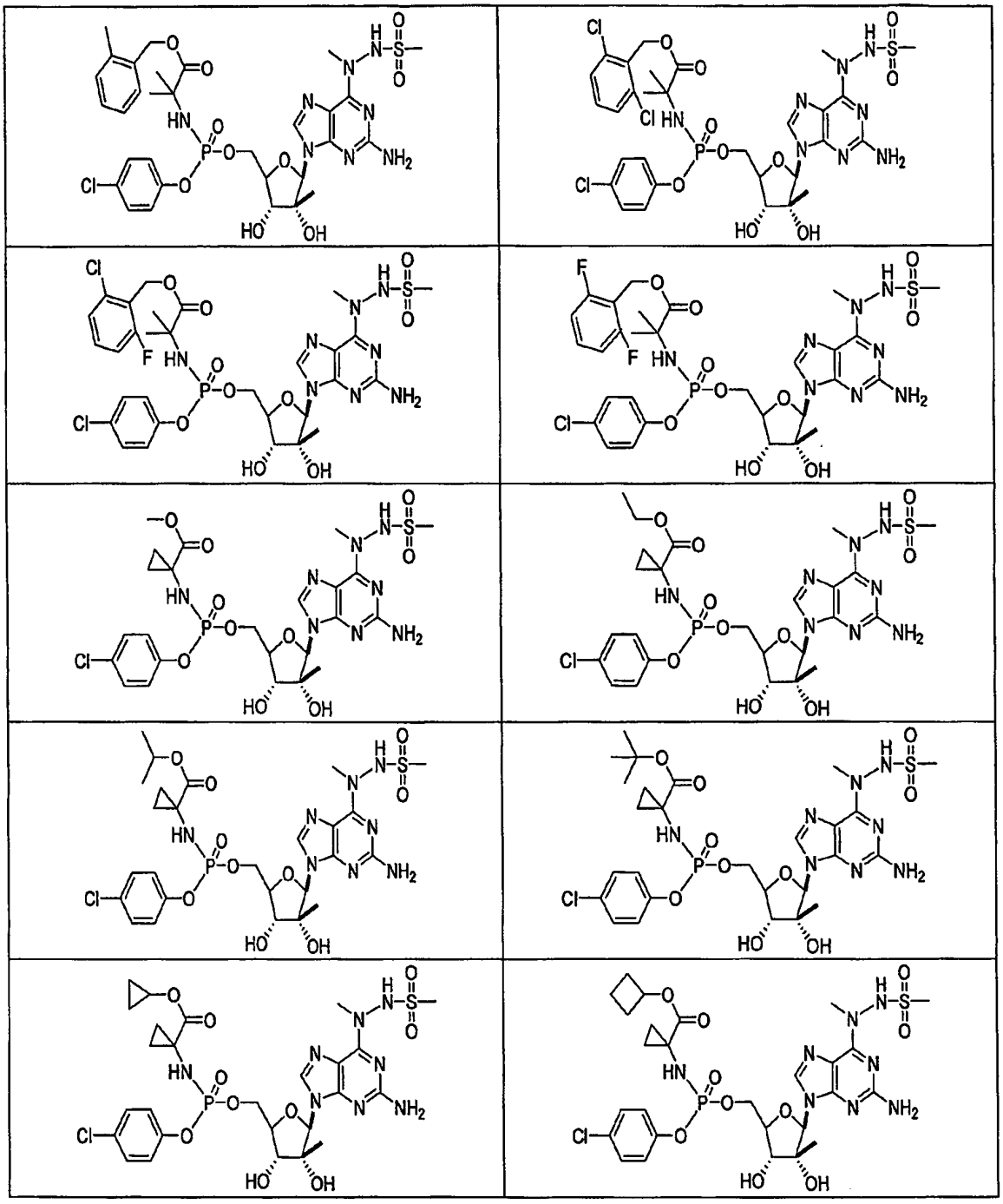
Table 3

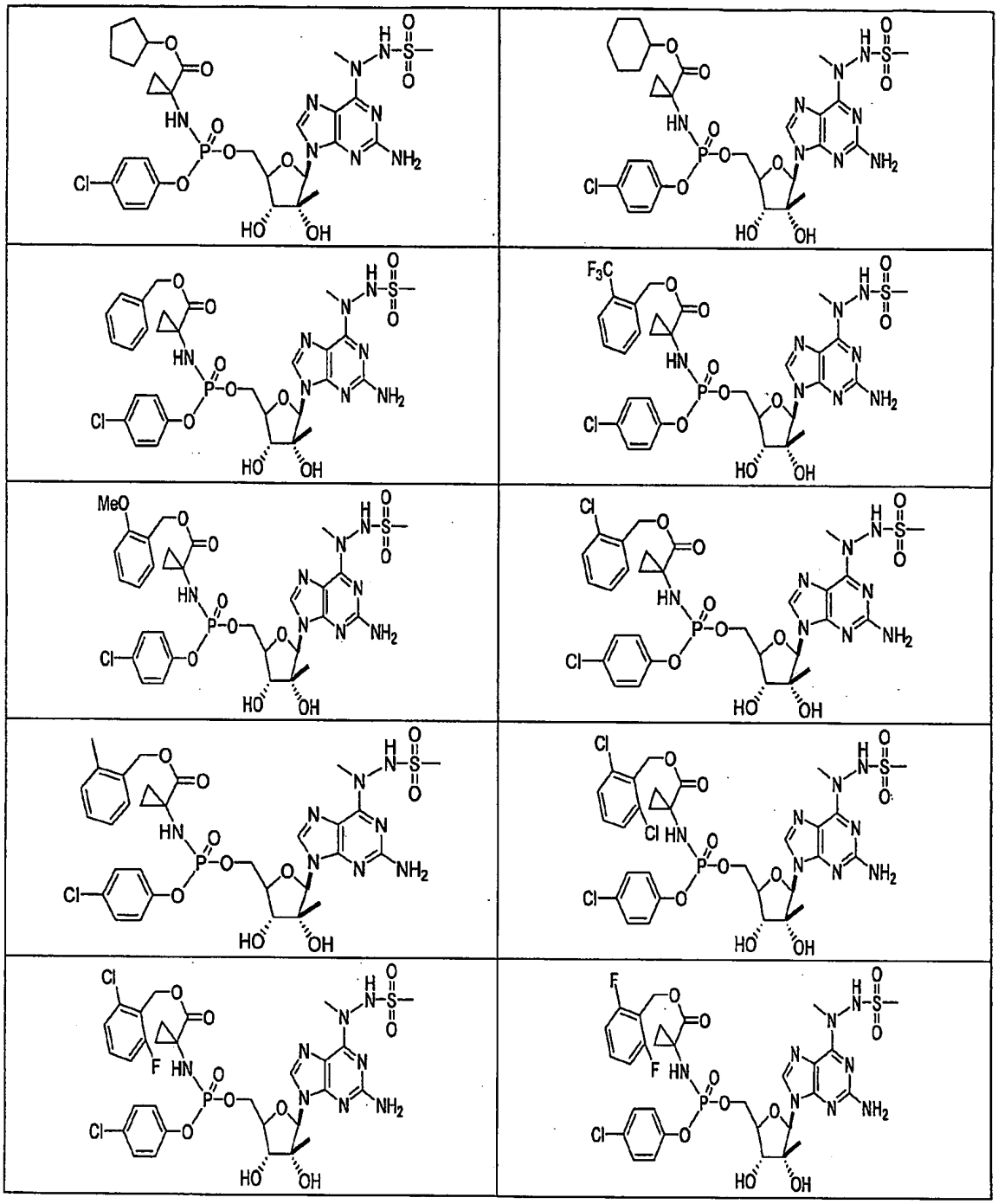
Contemplated Compounds

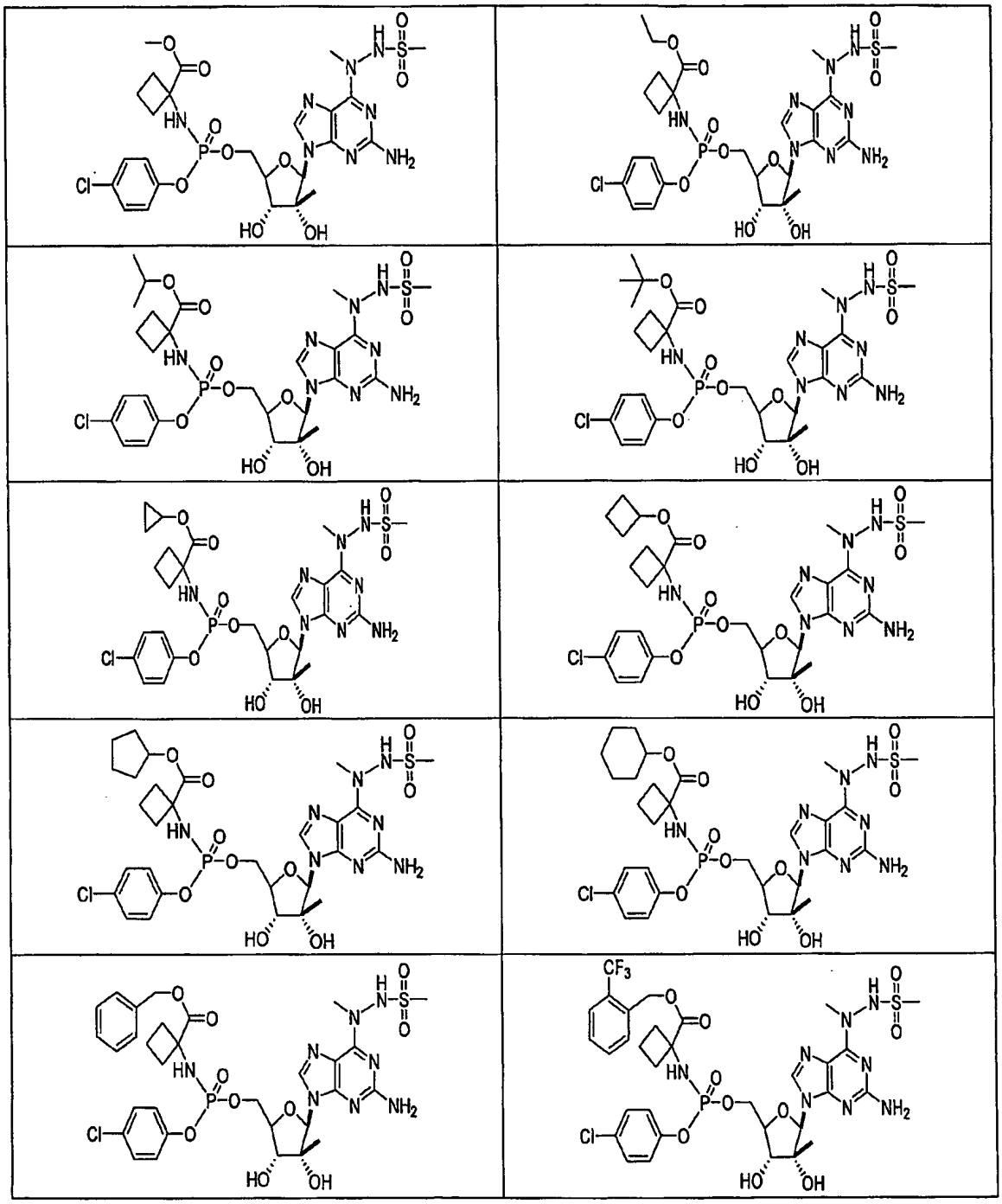


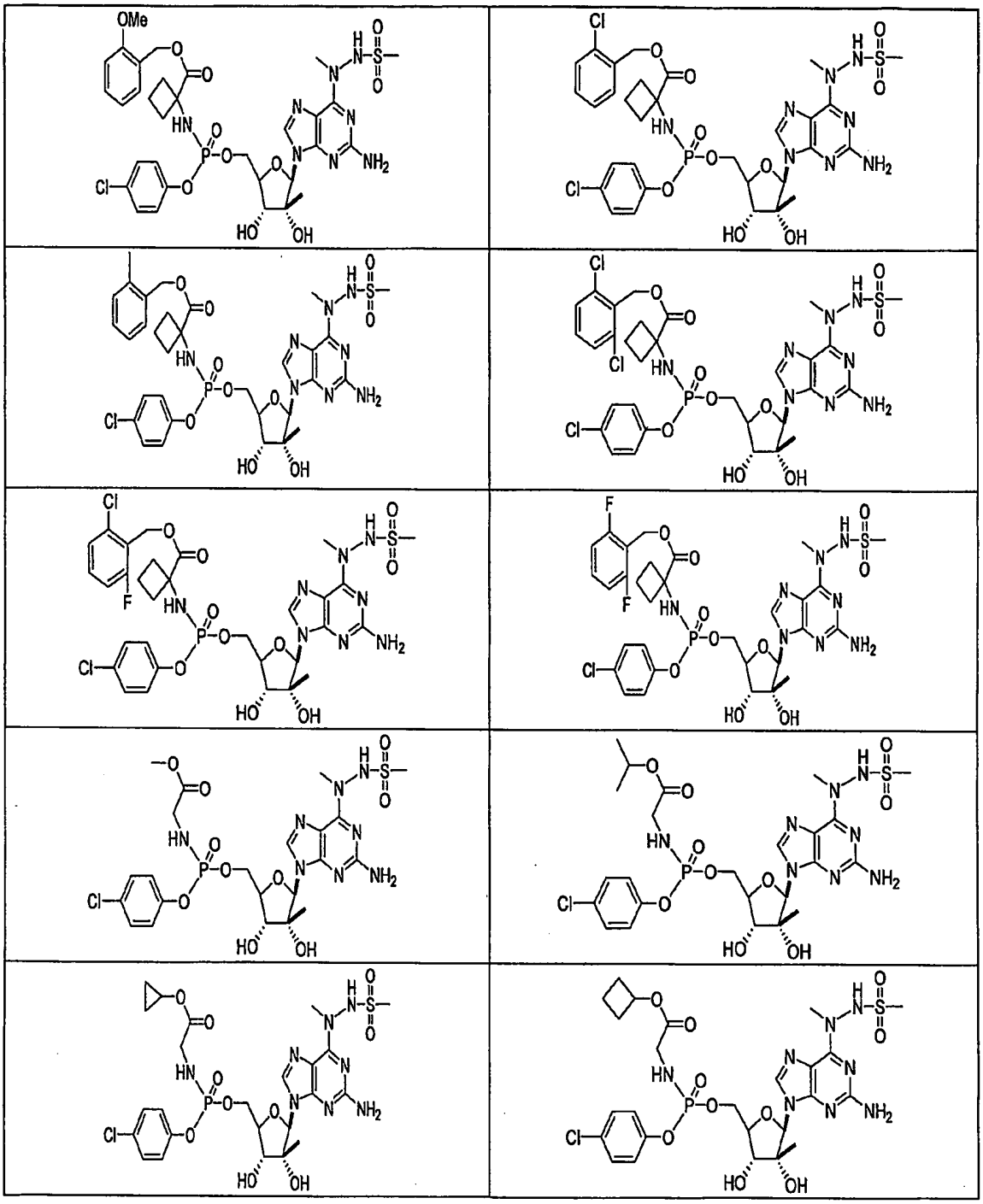


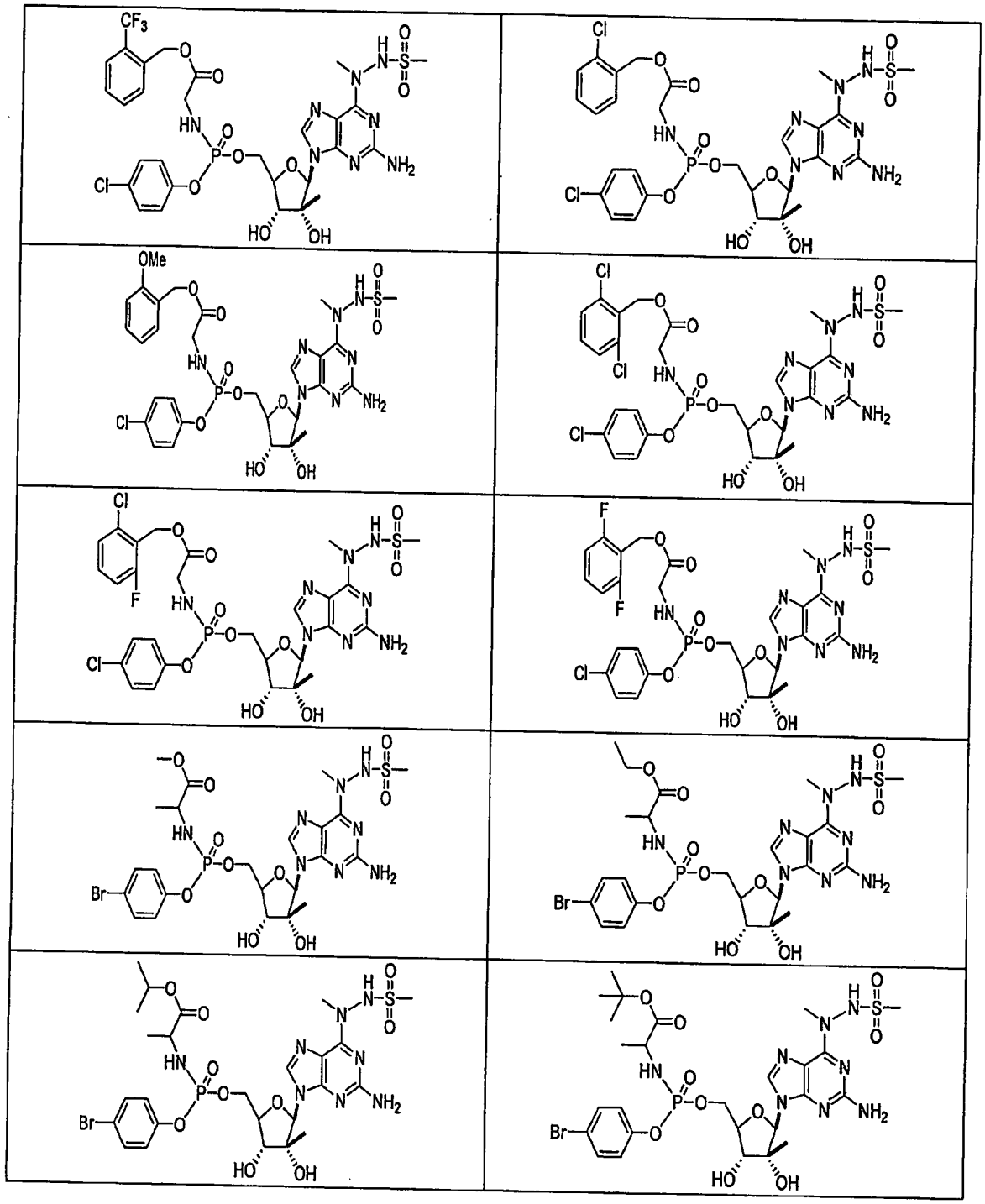


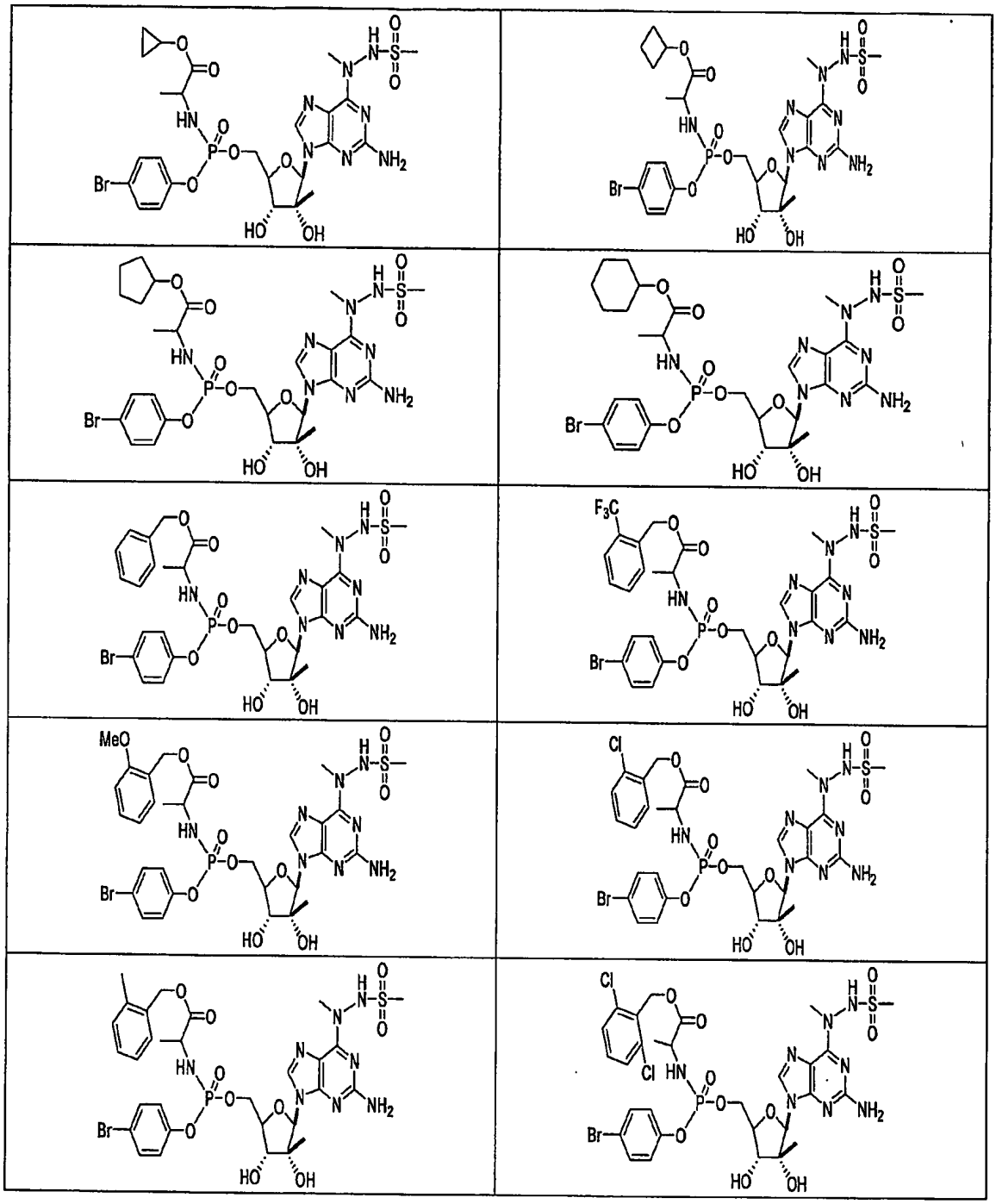


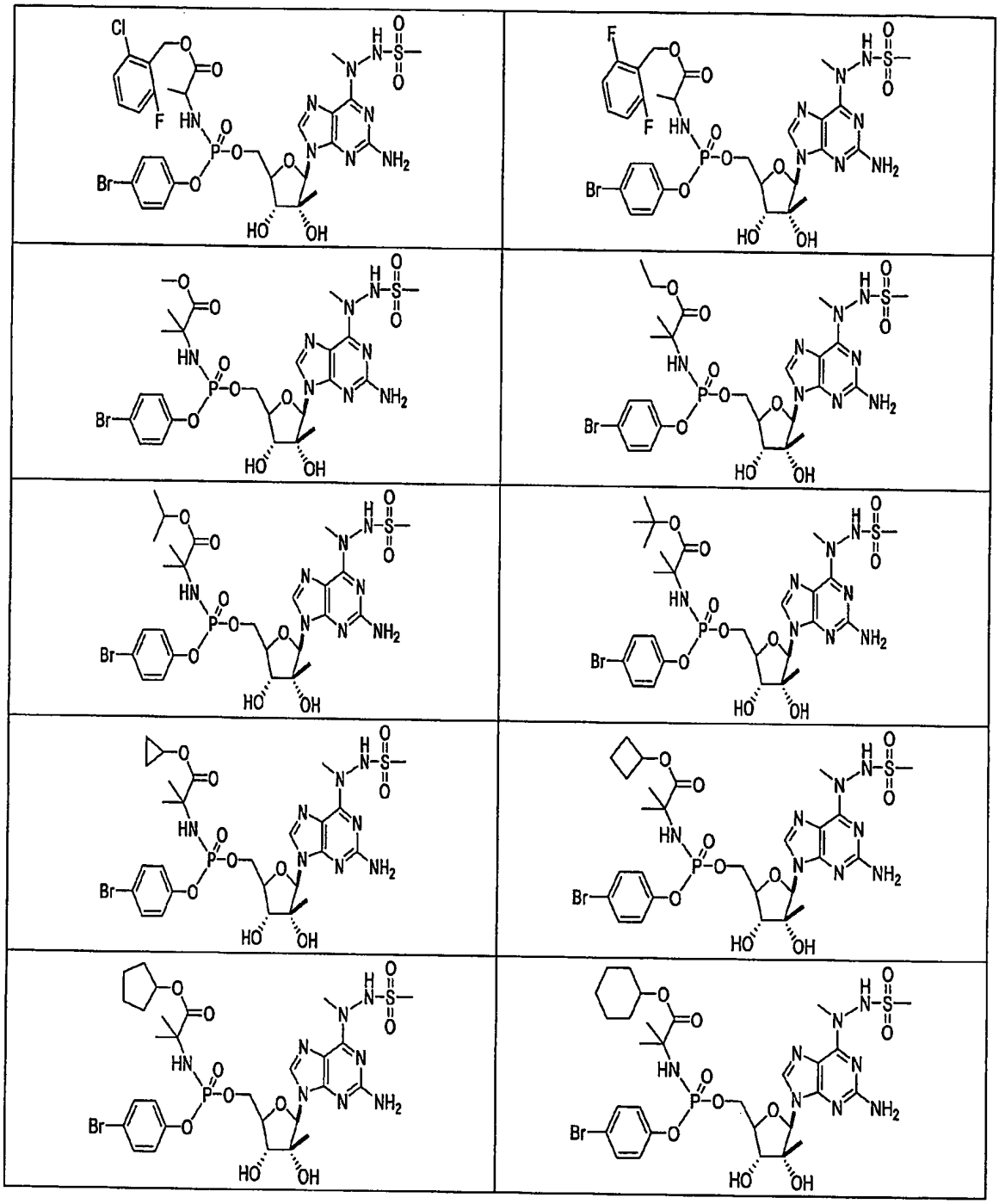


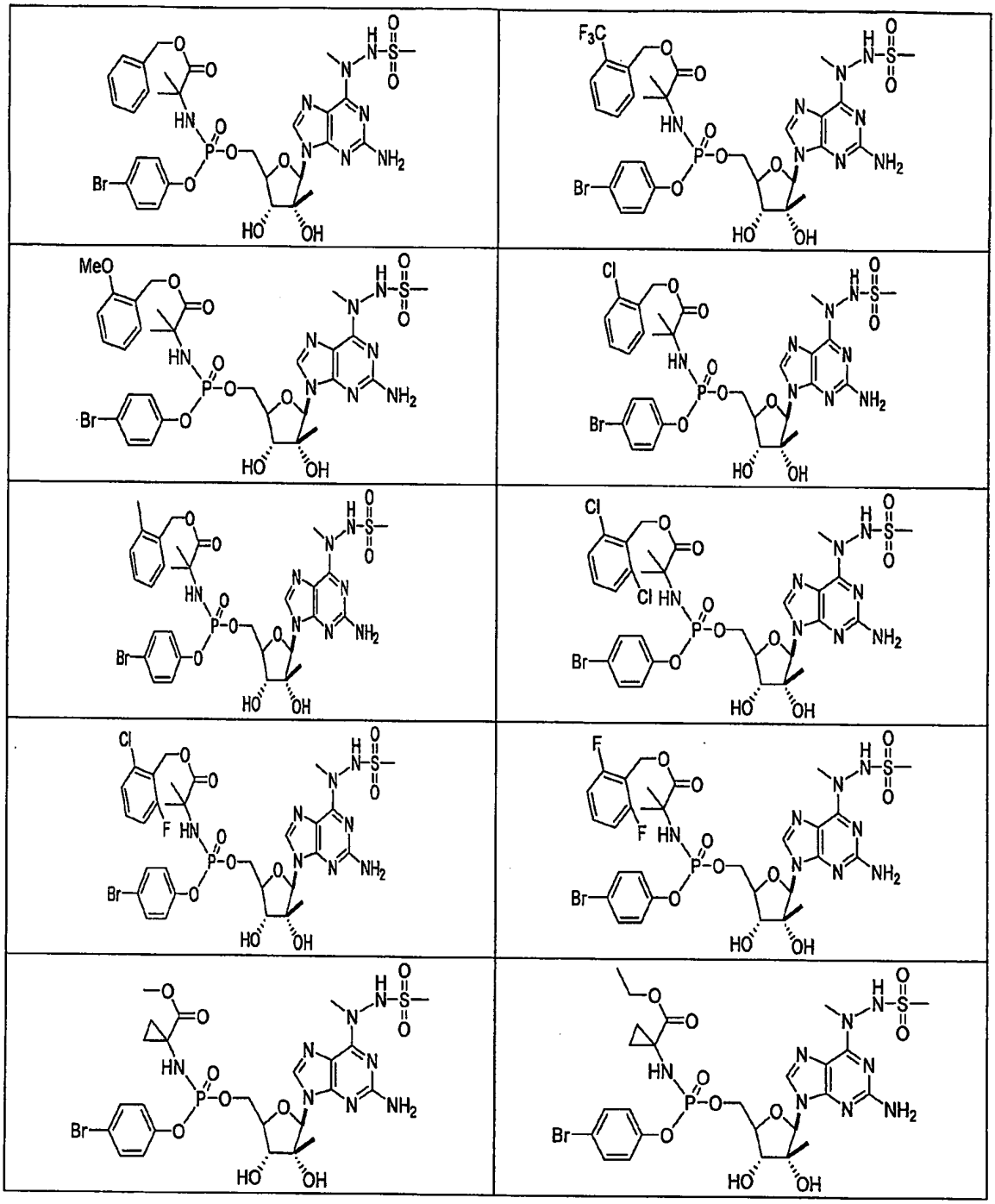


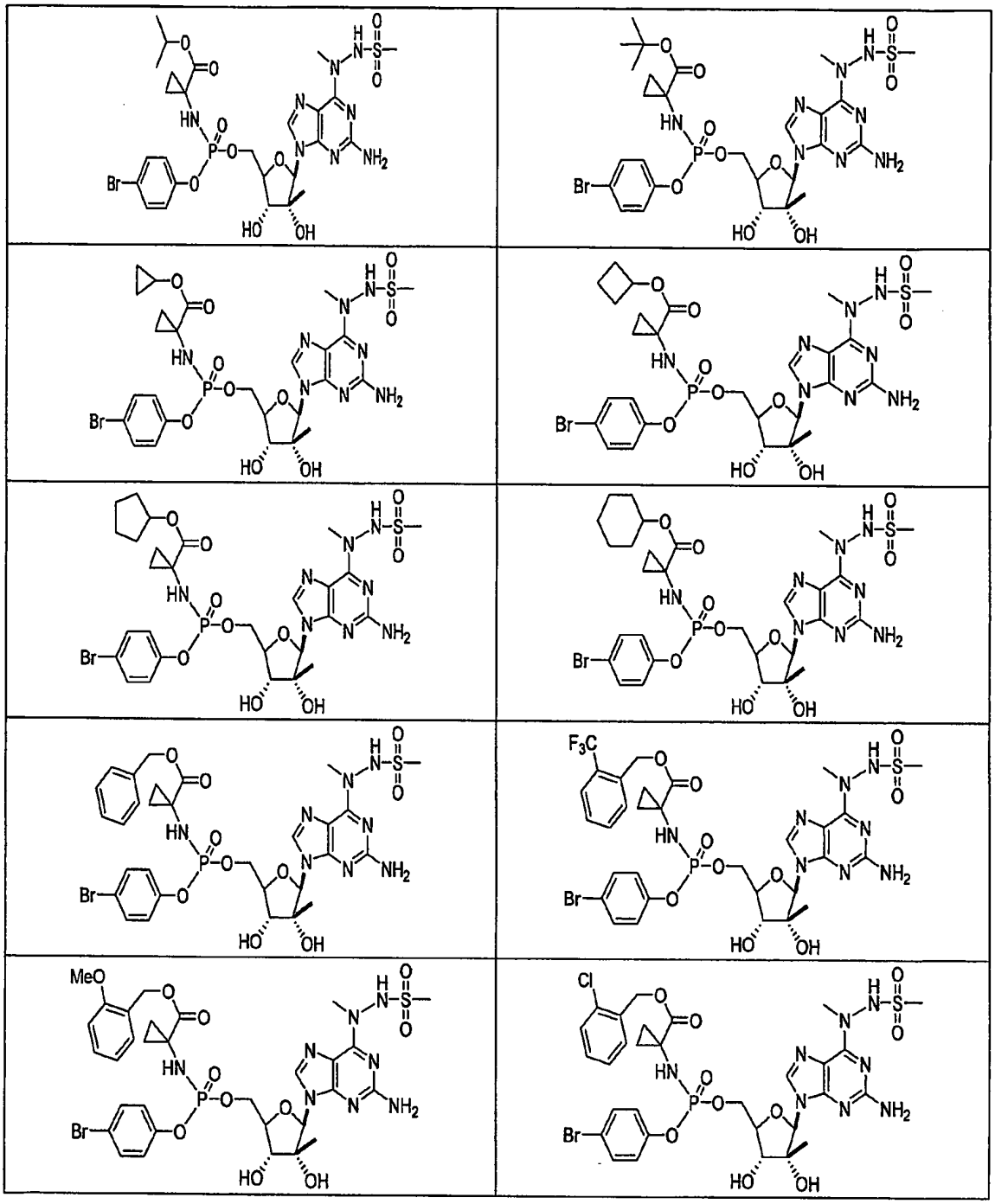


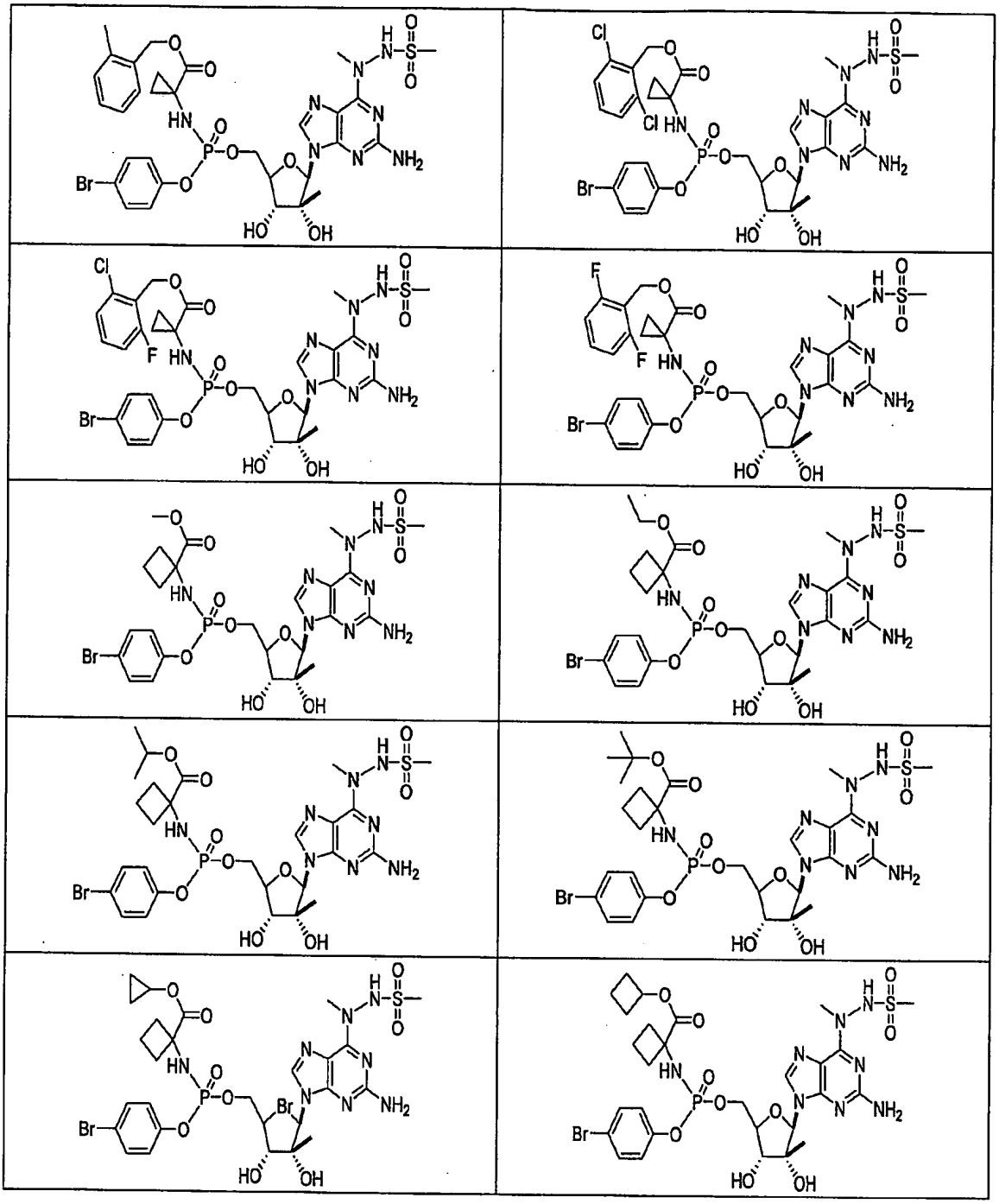


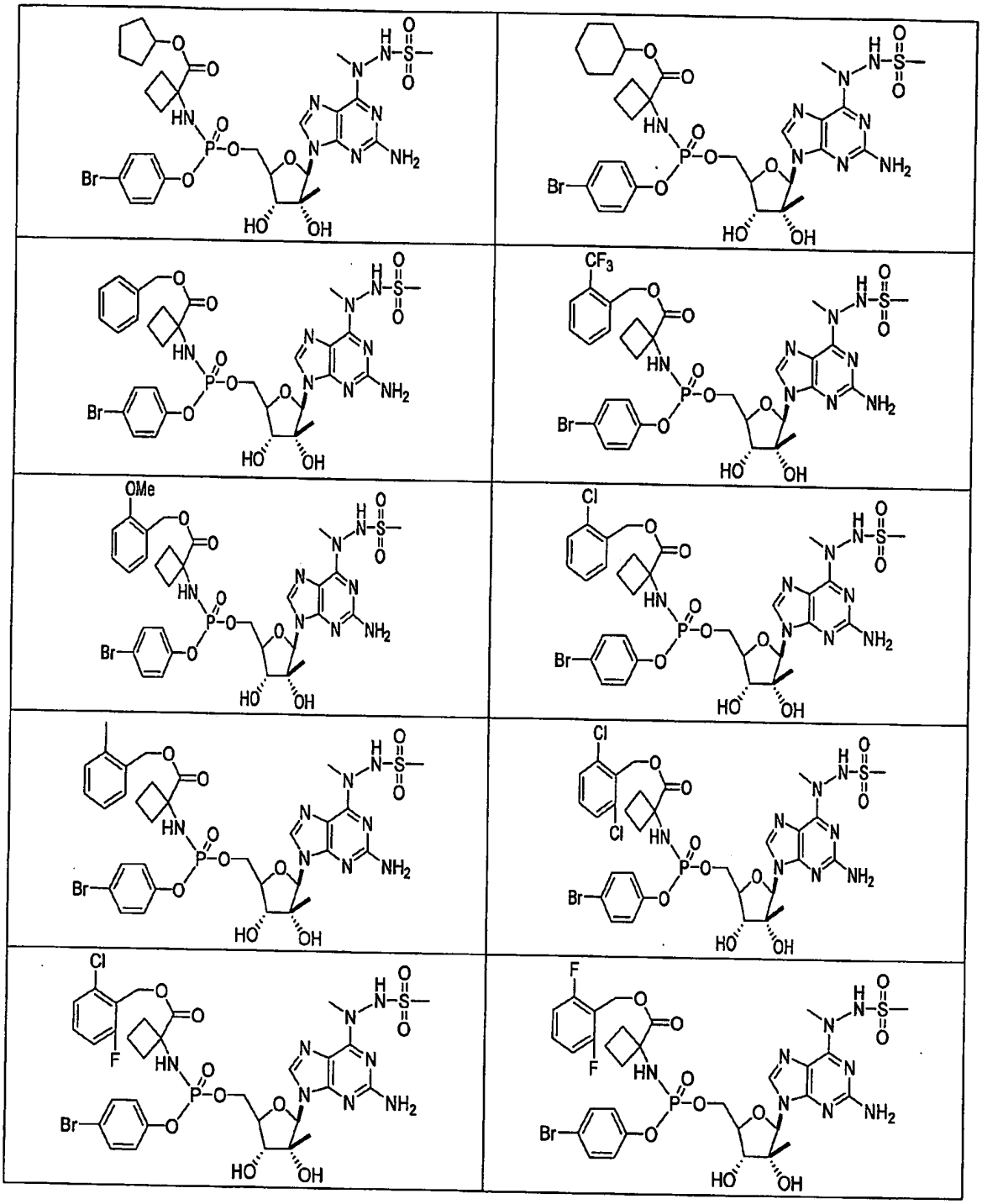


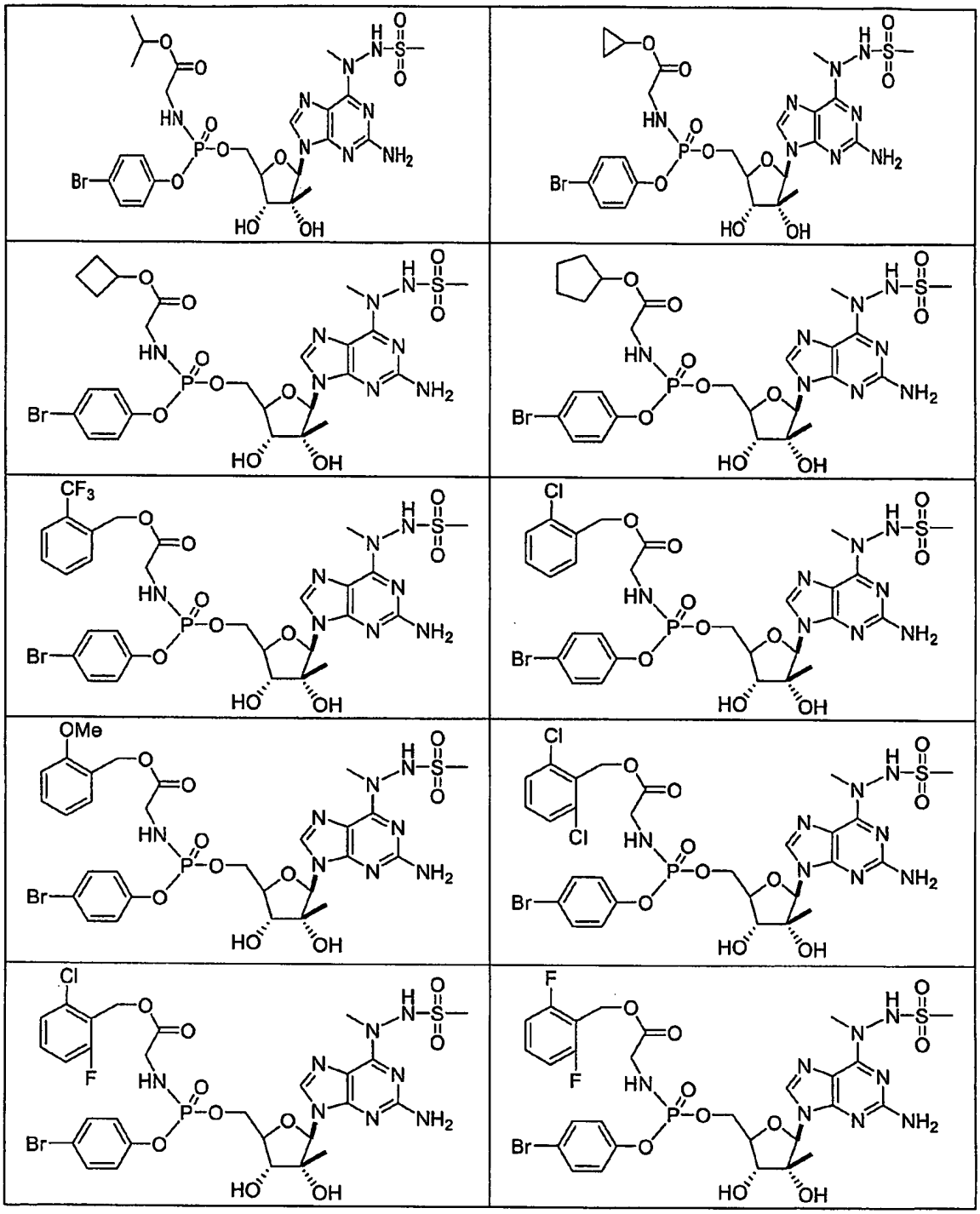


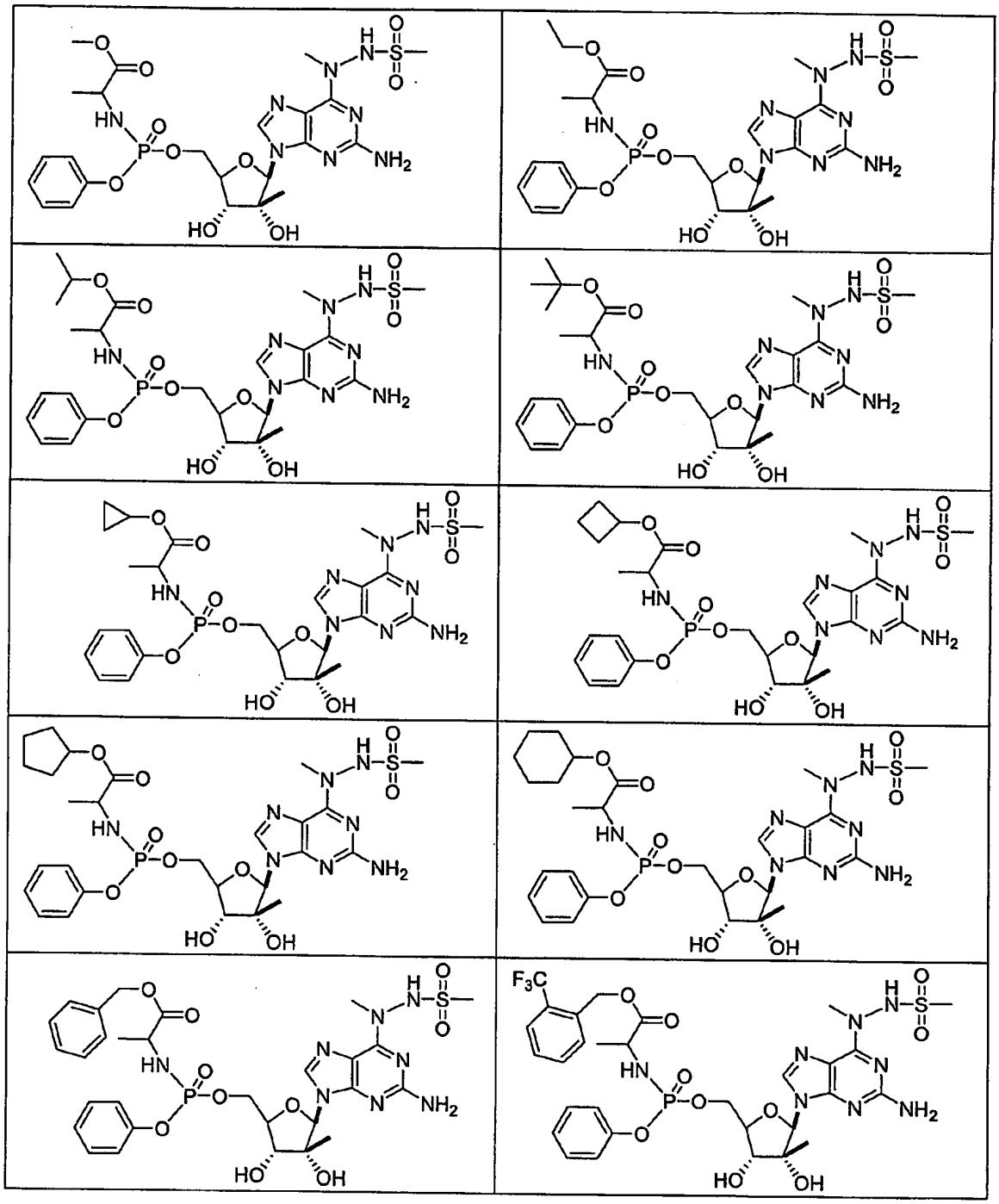


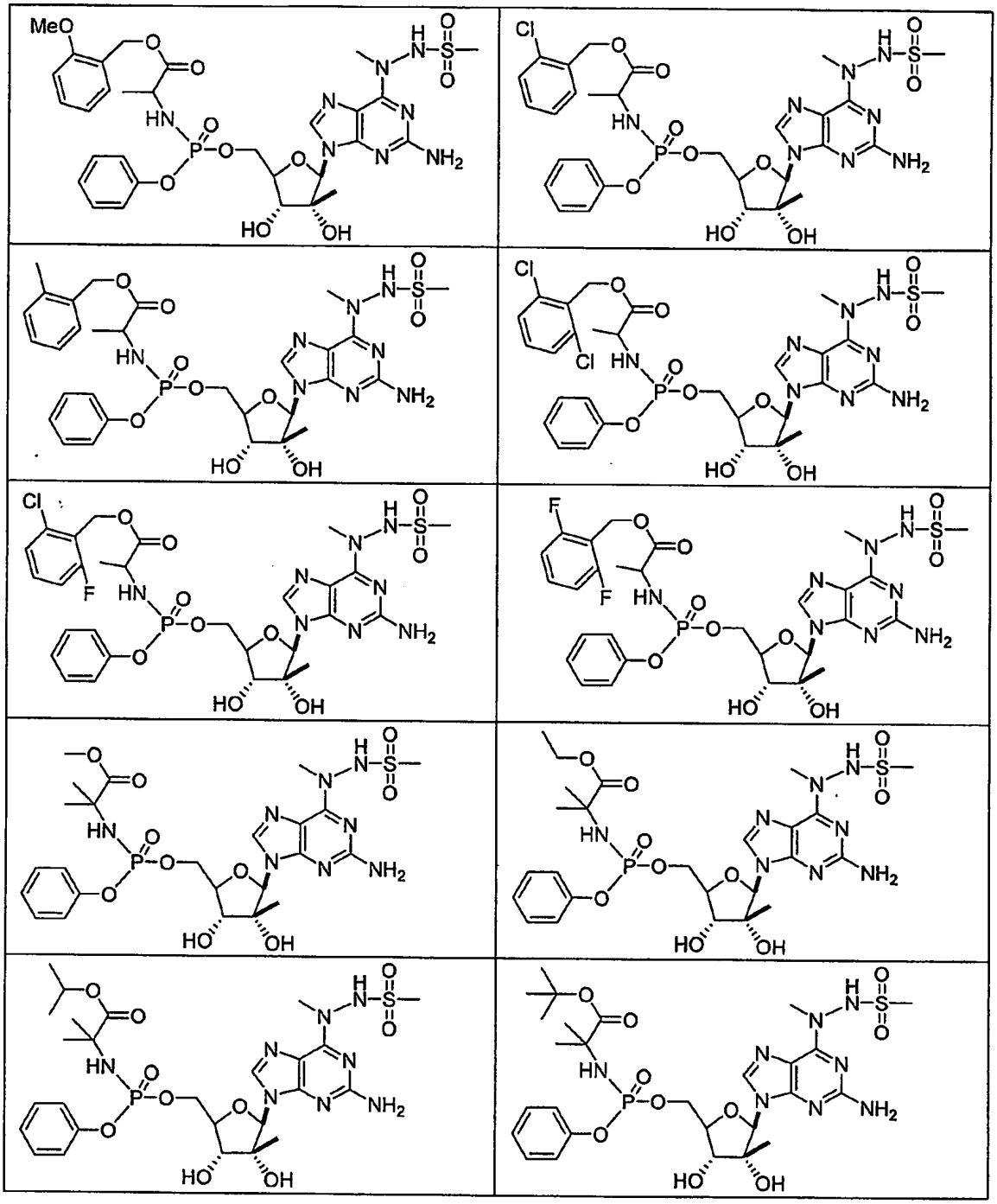


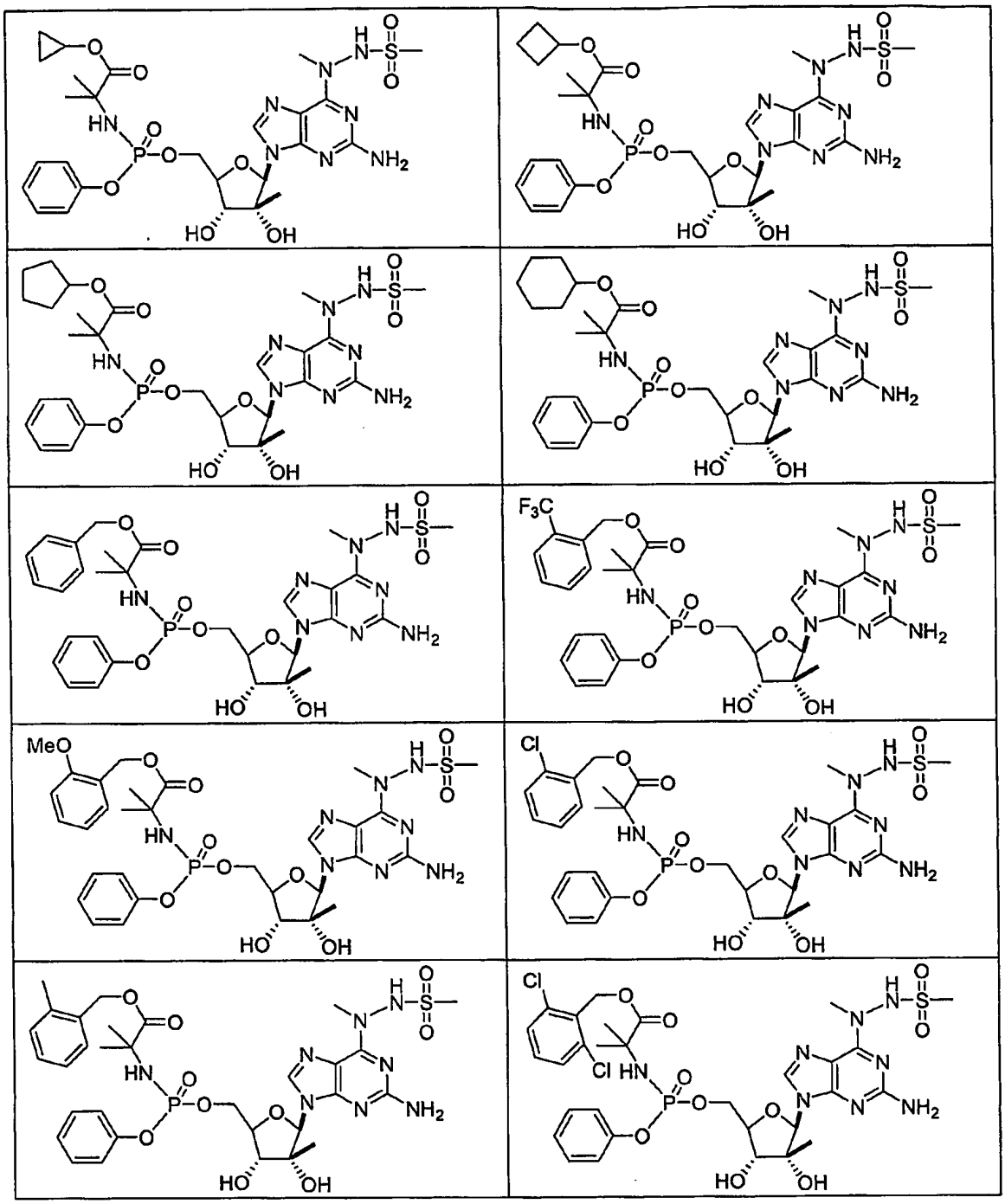


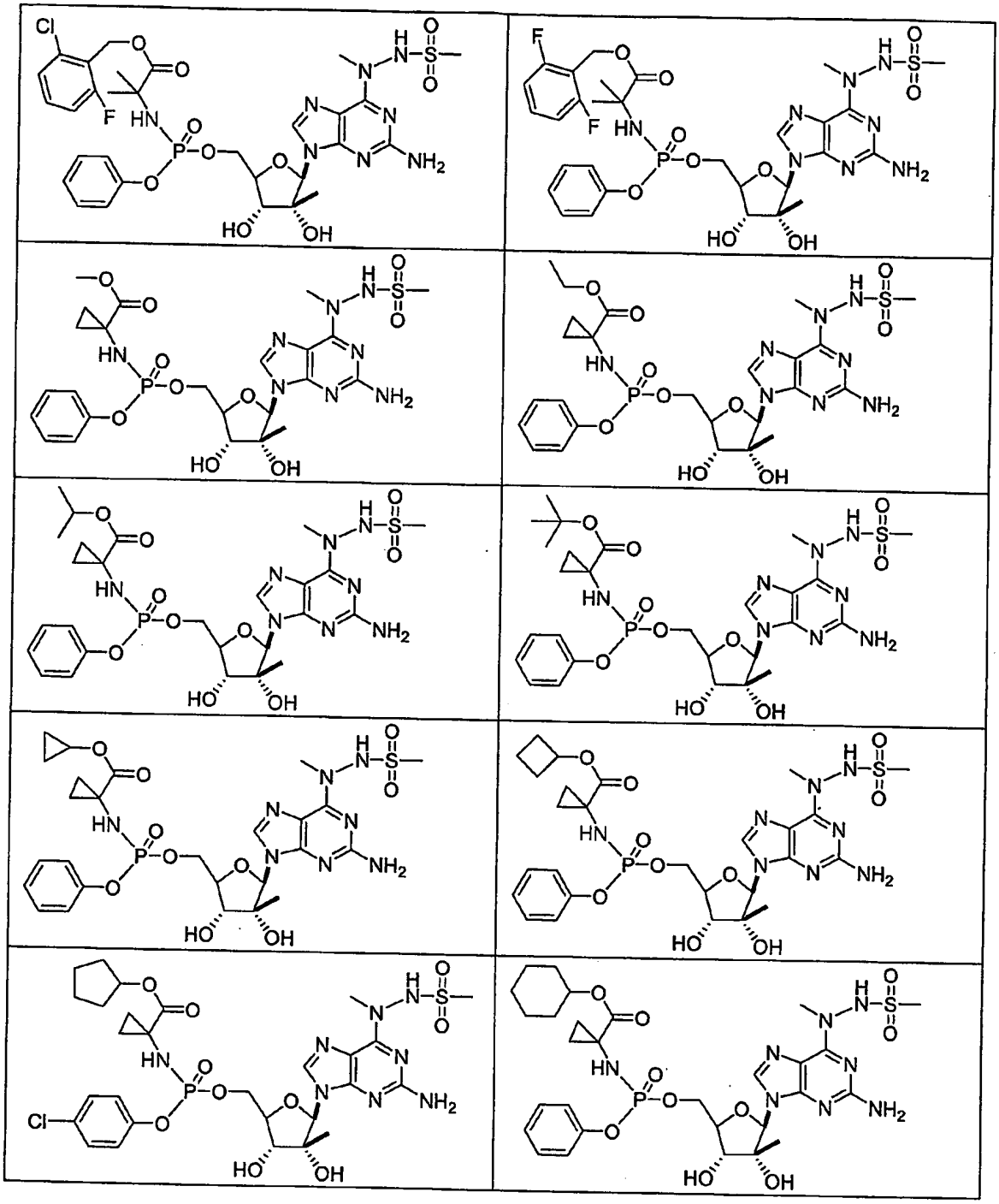


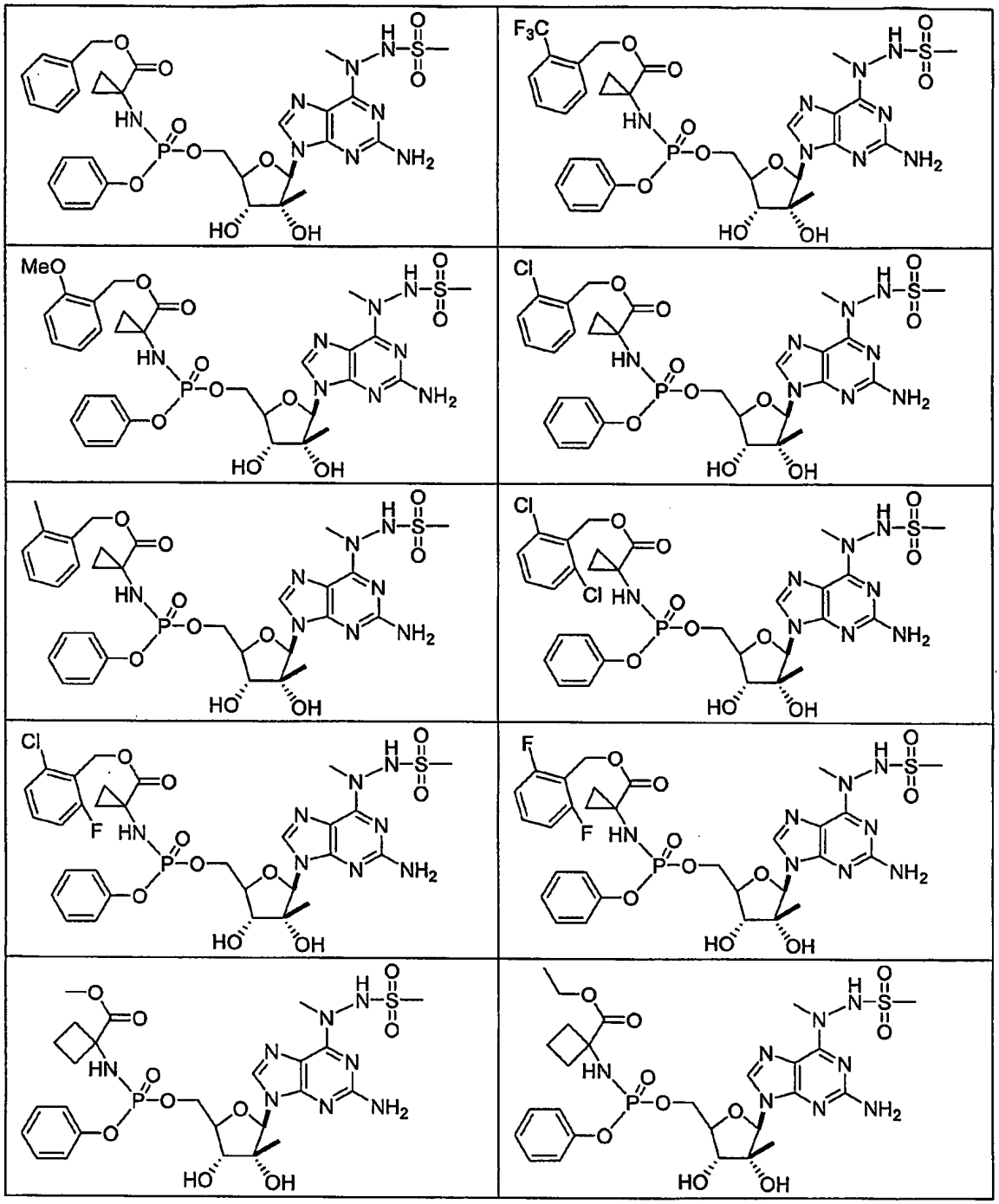


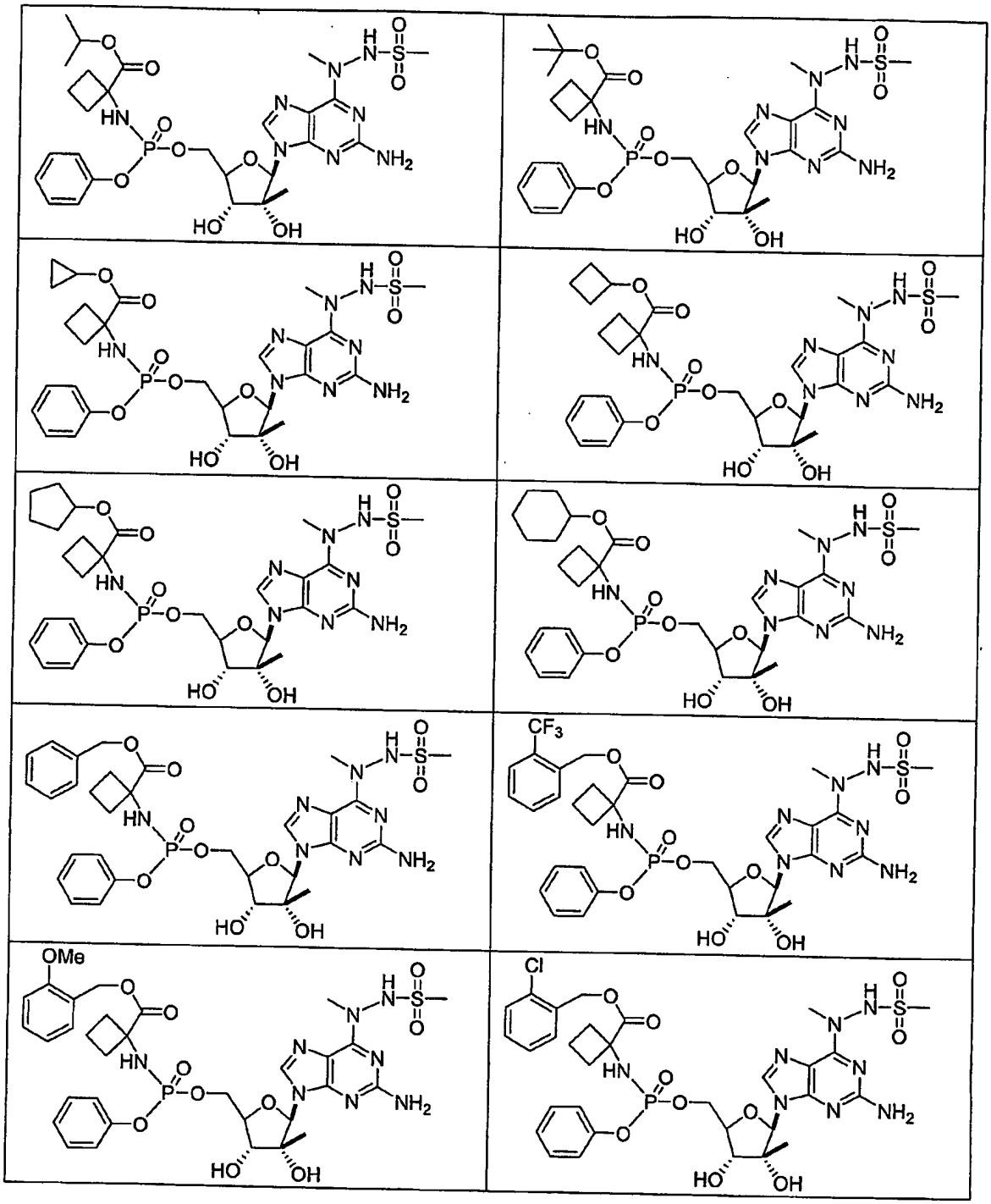


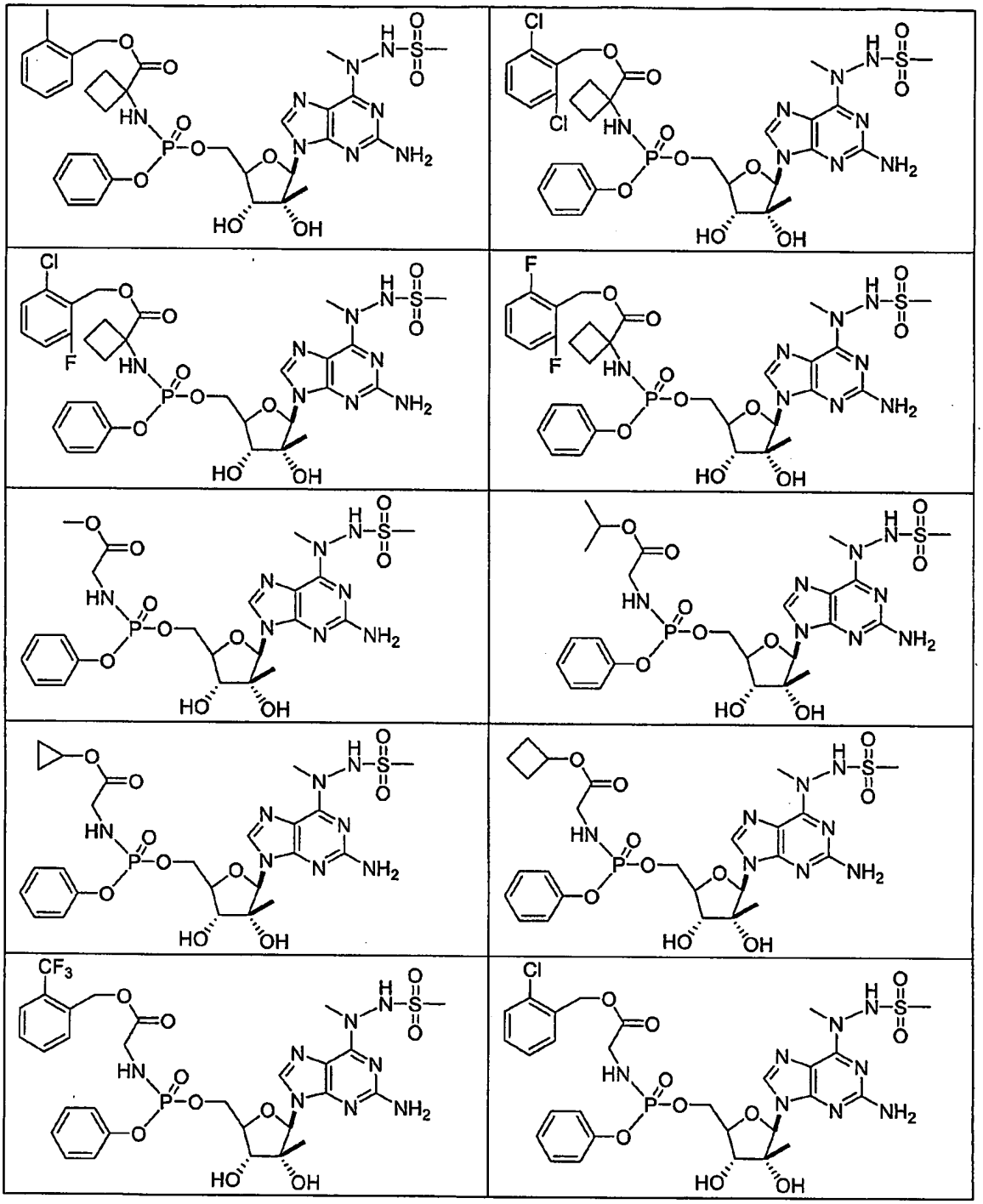


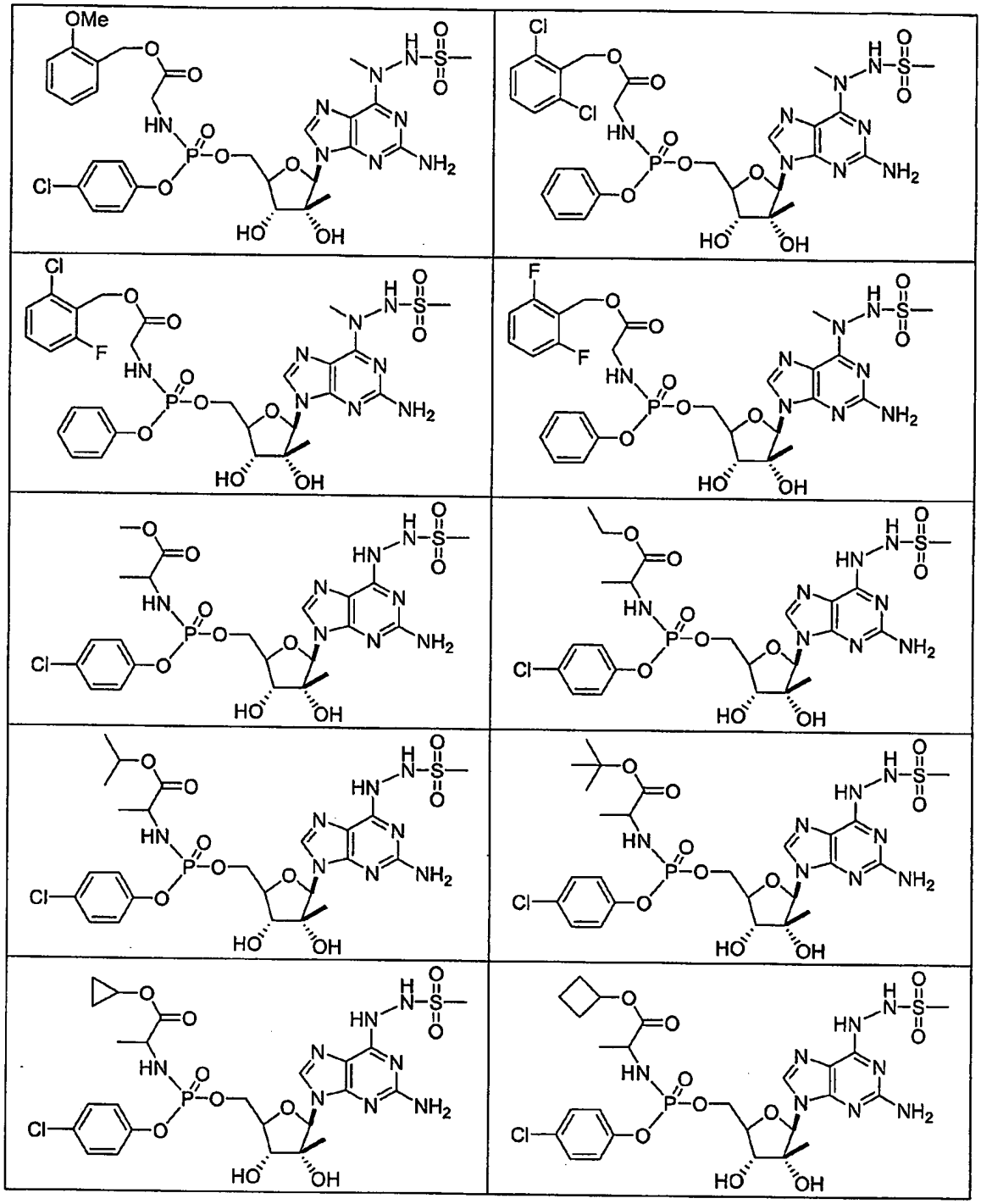


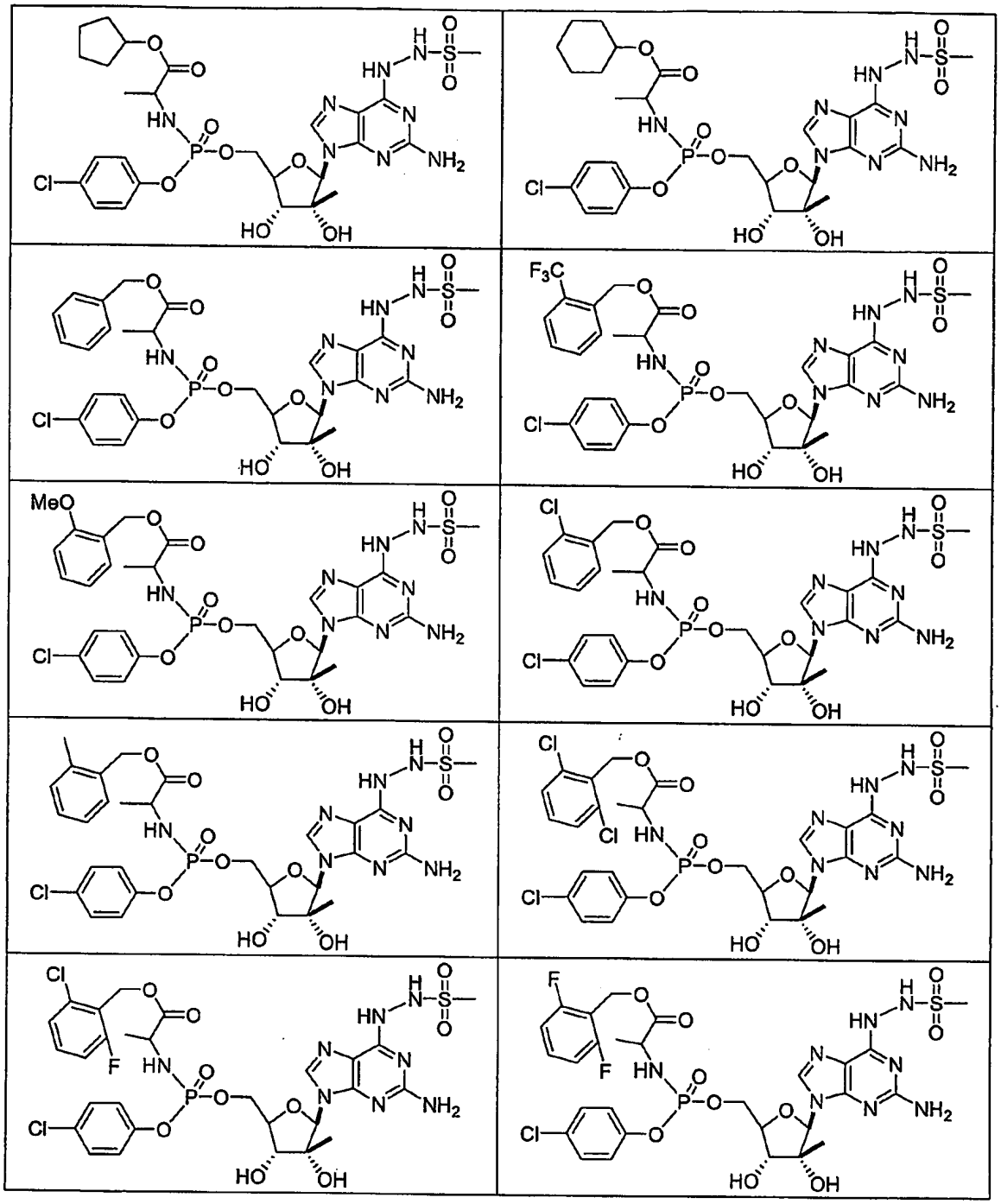


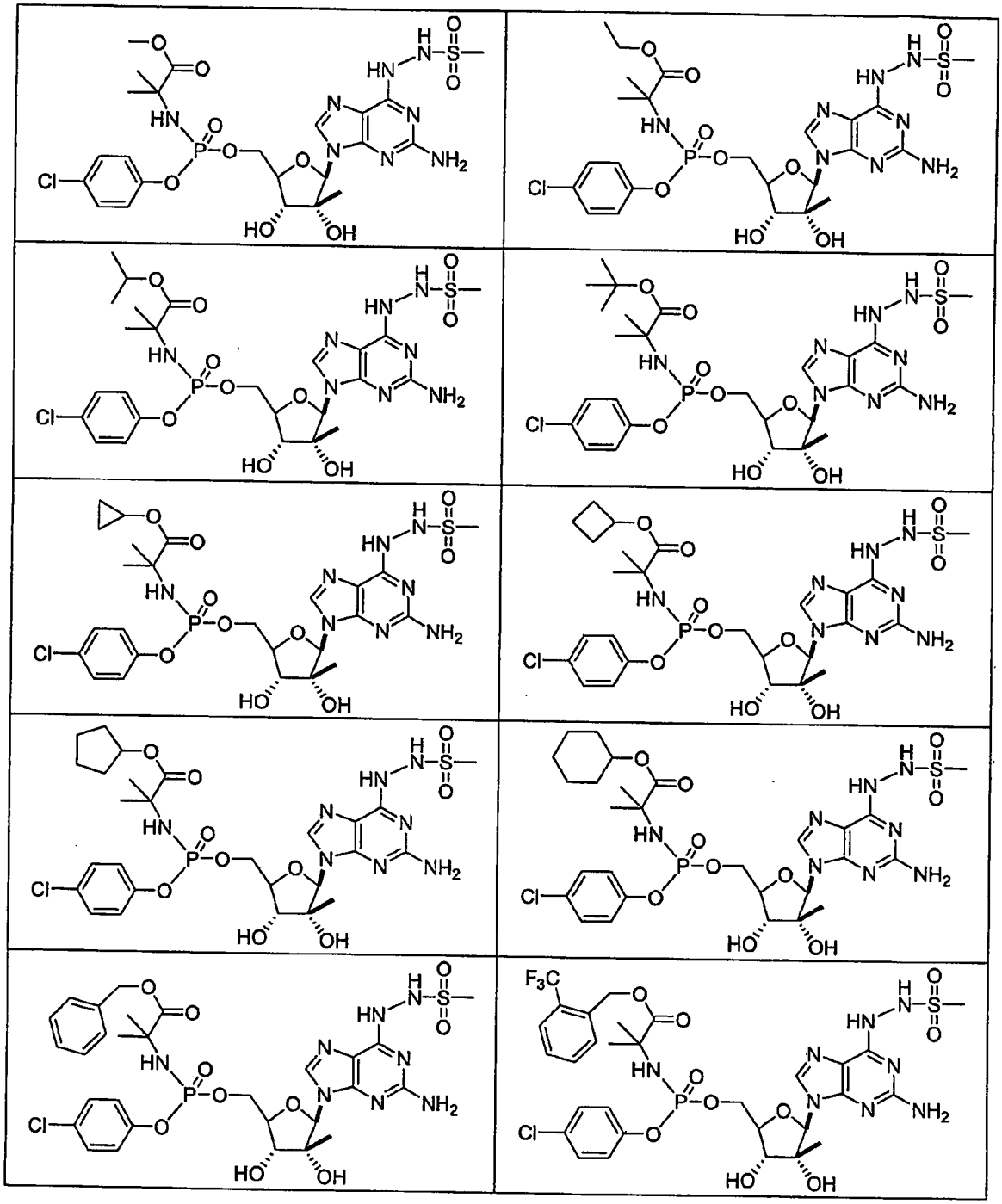


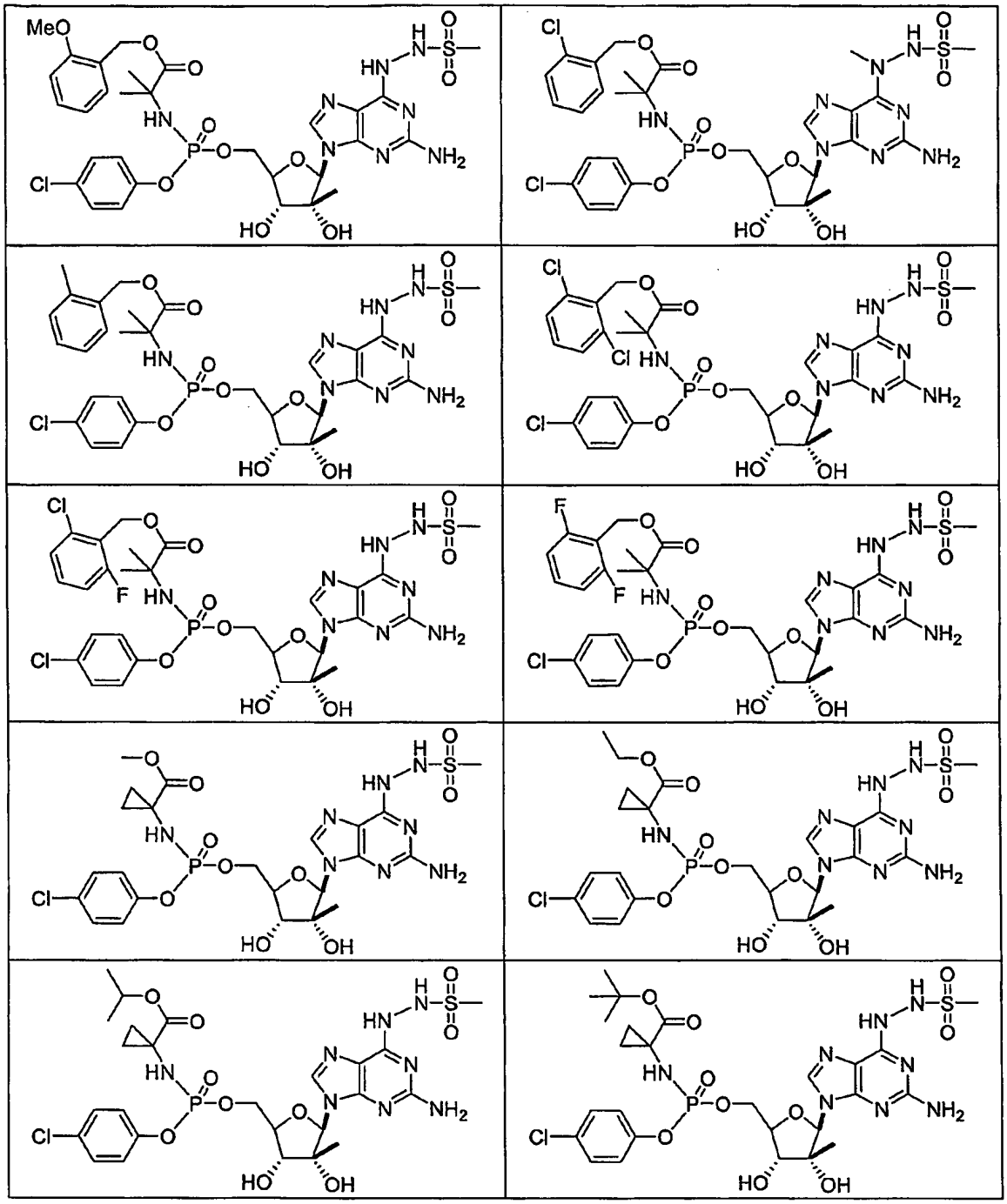


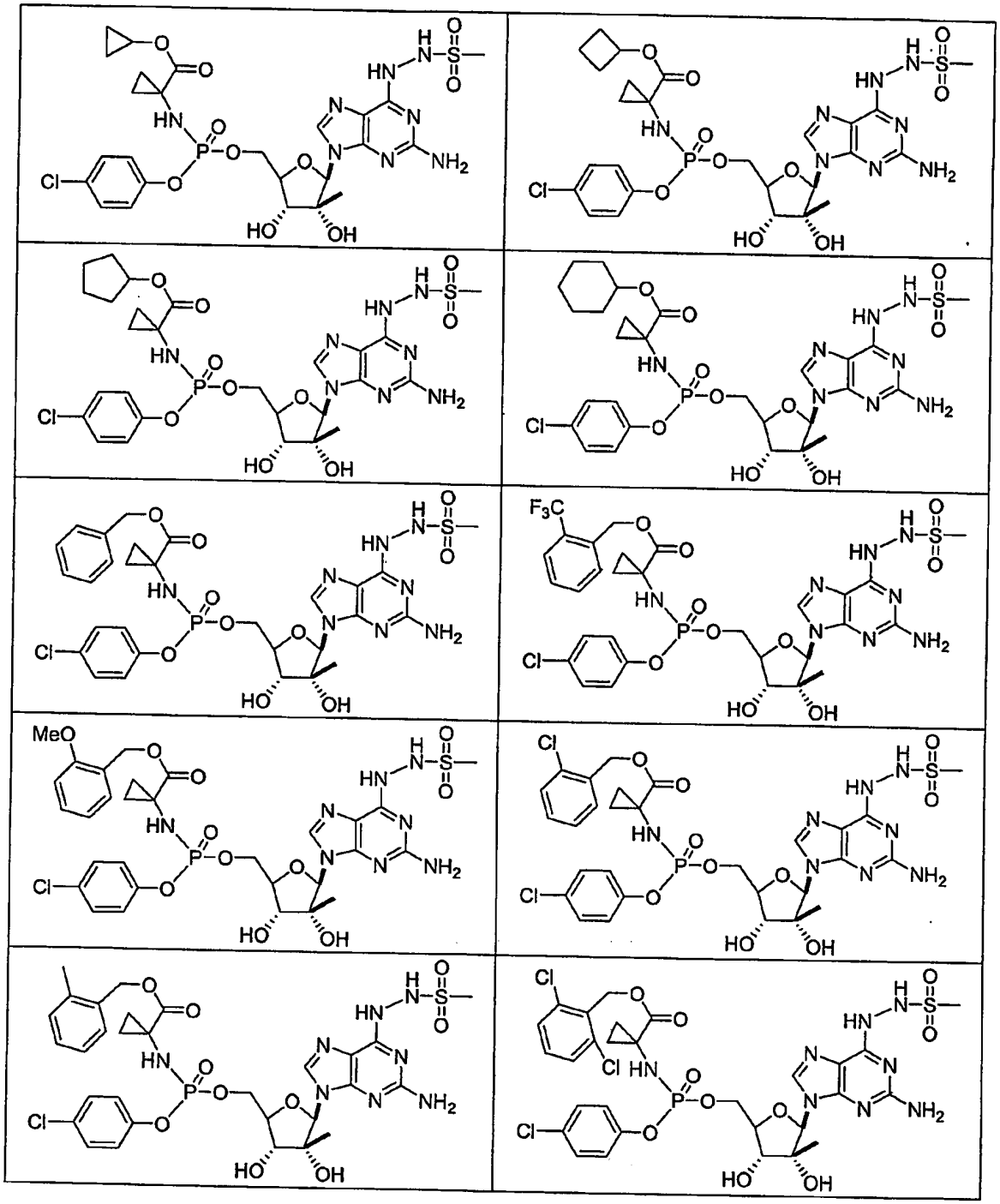


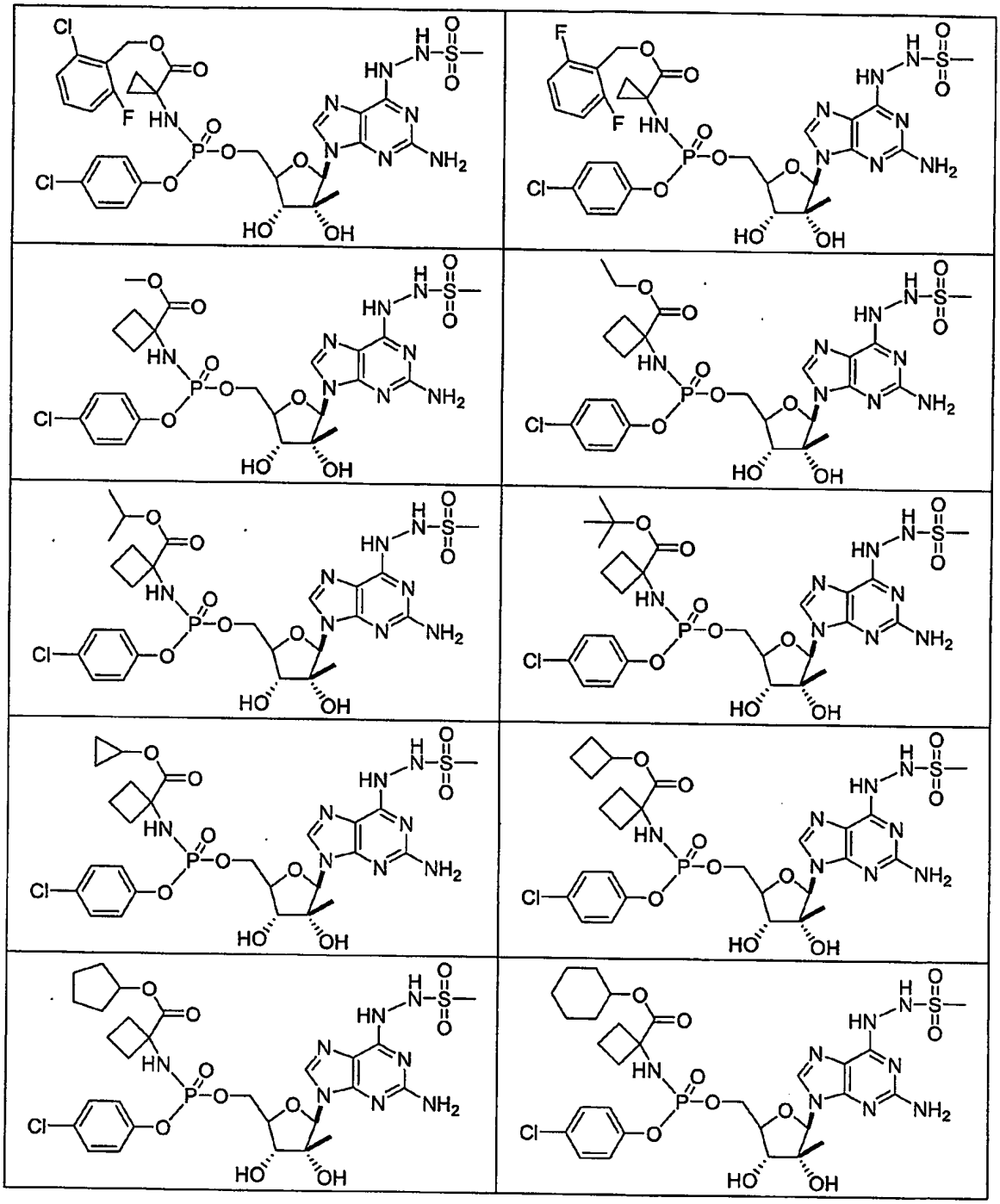


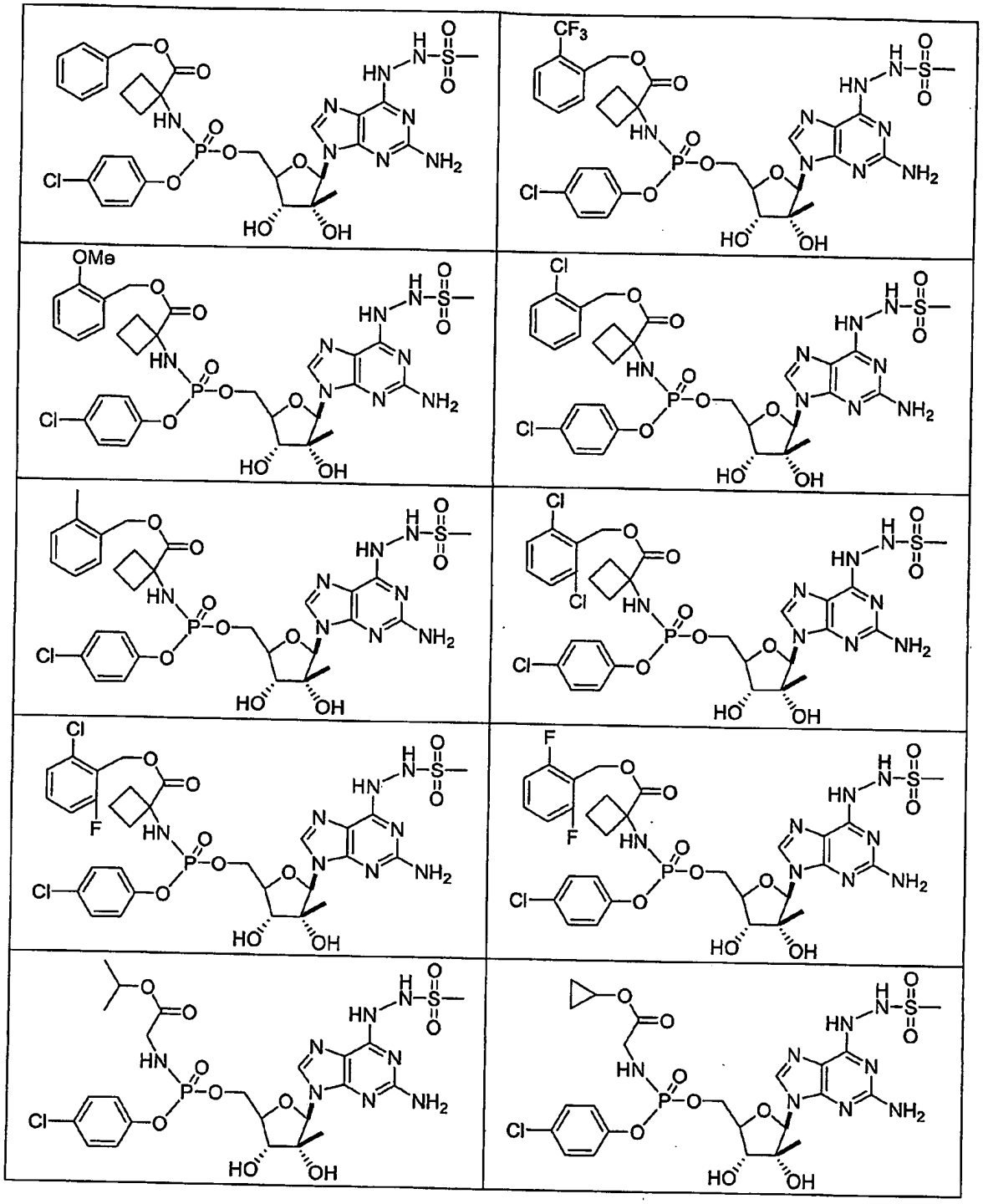


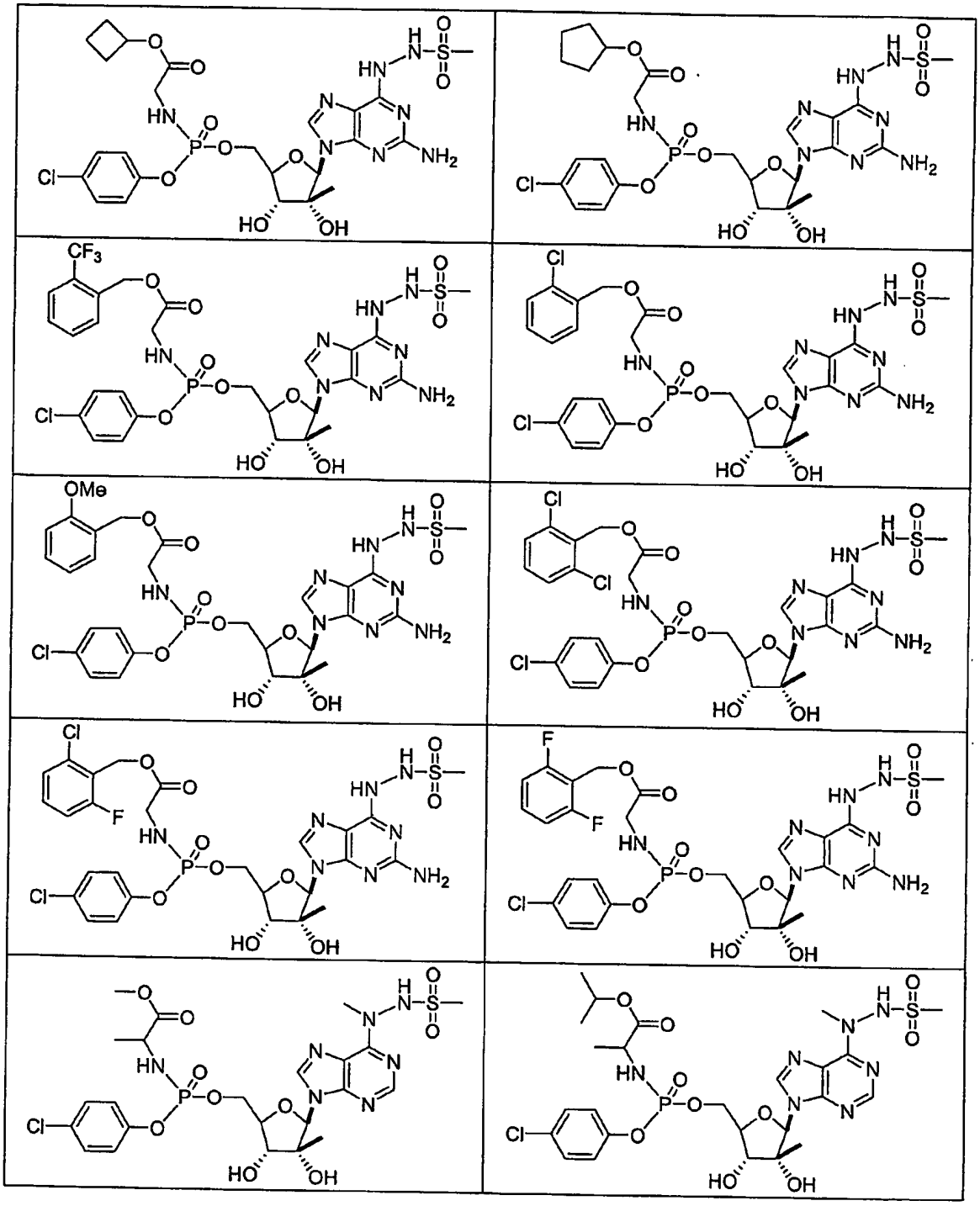


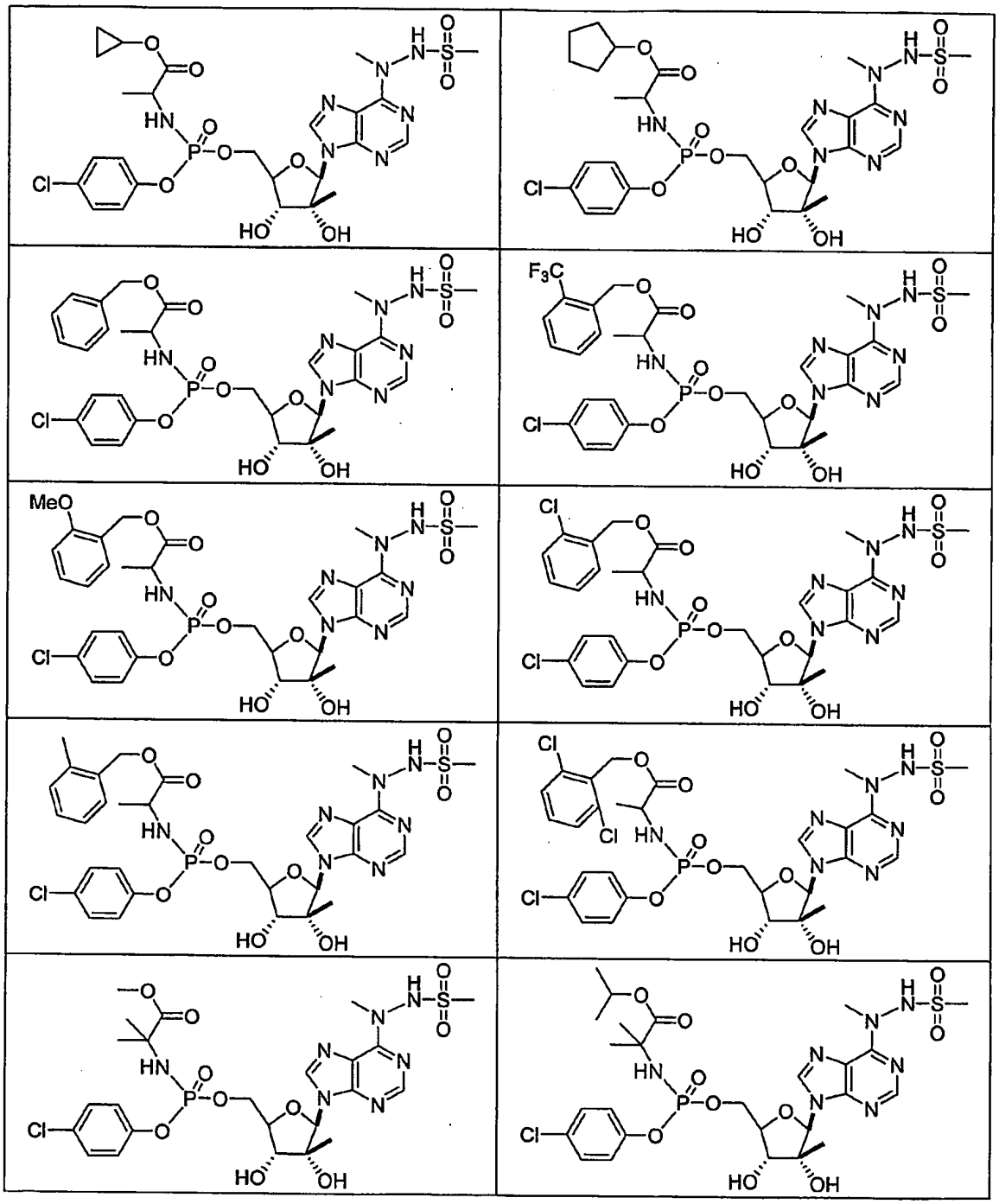


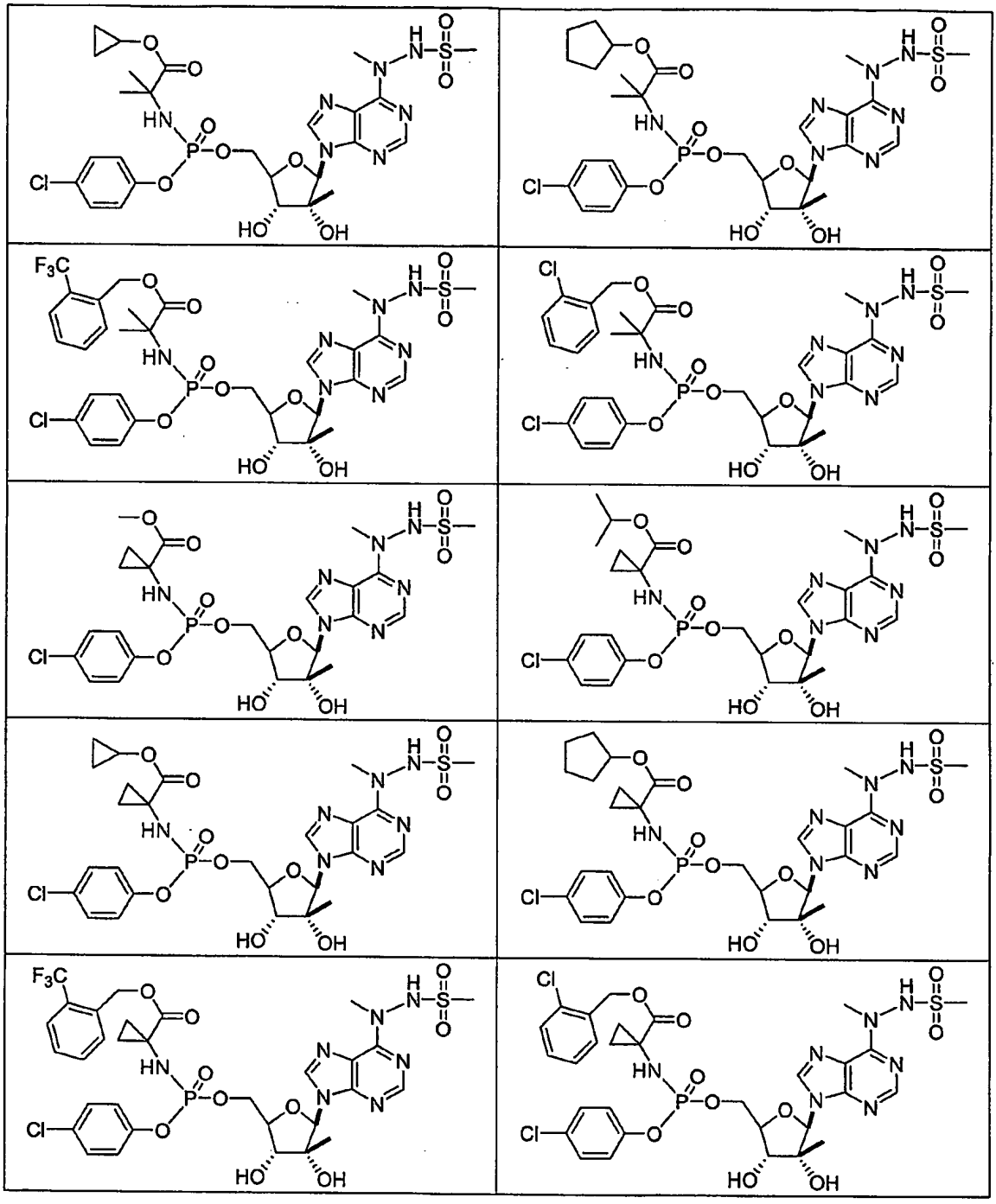


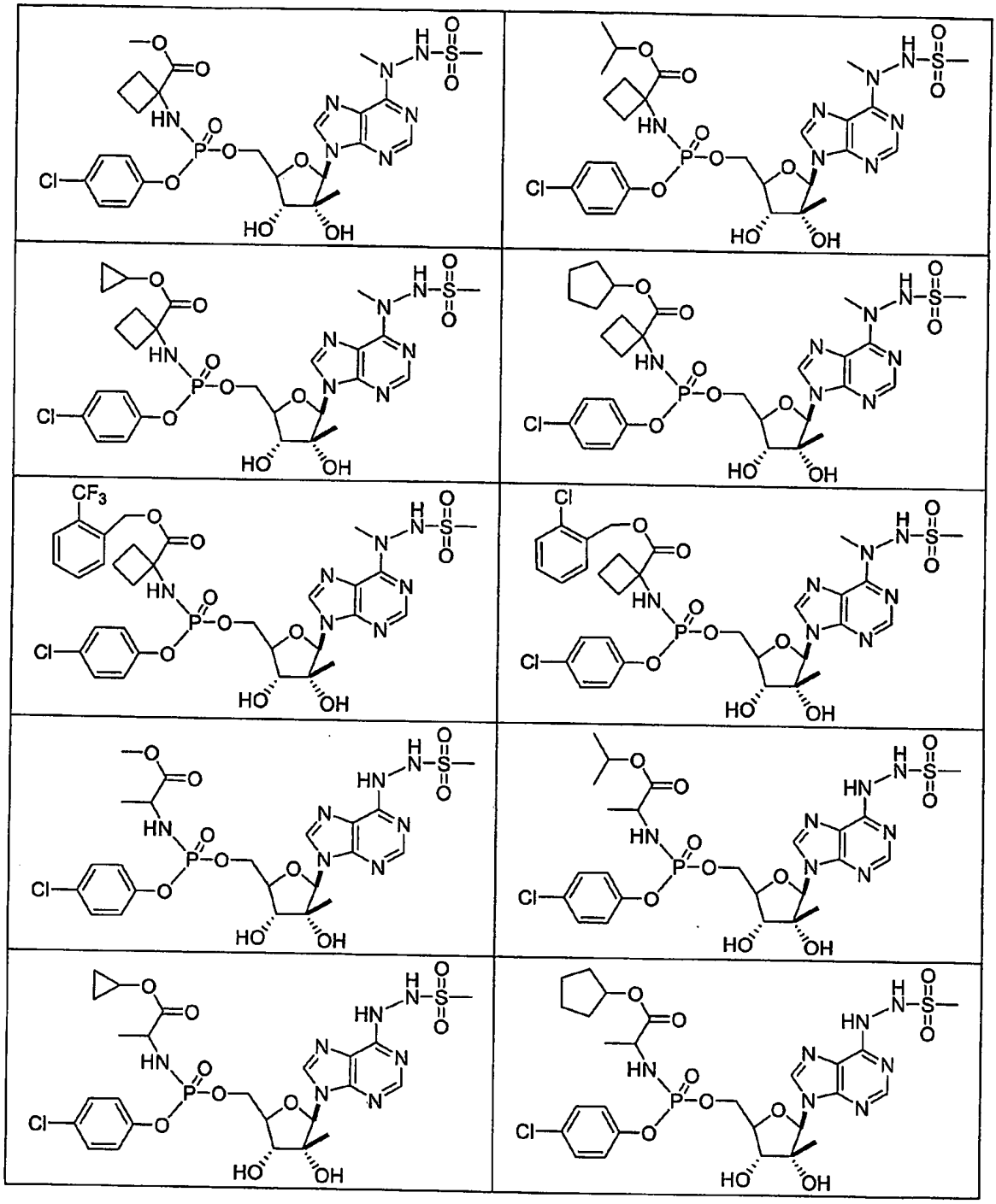


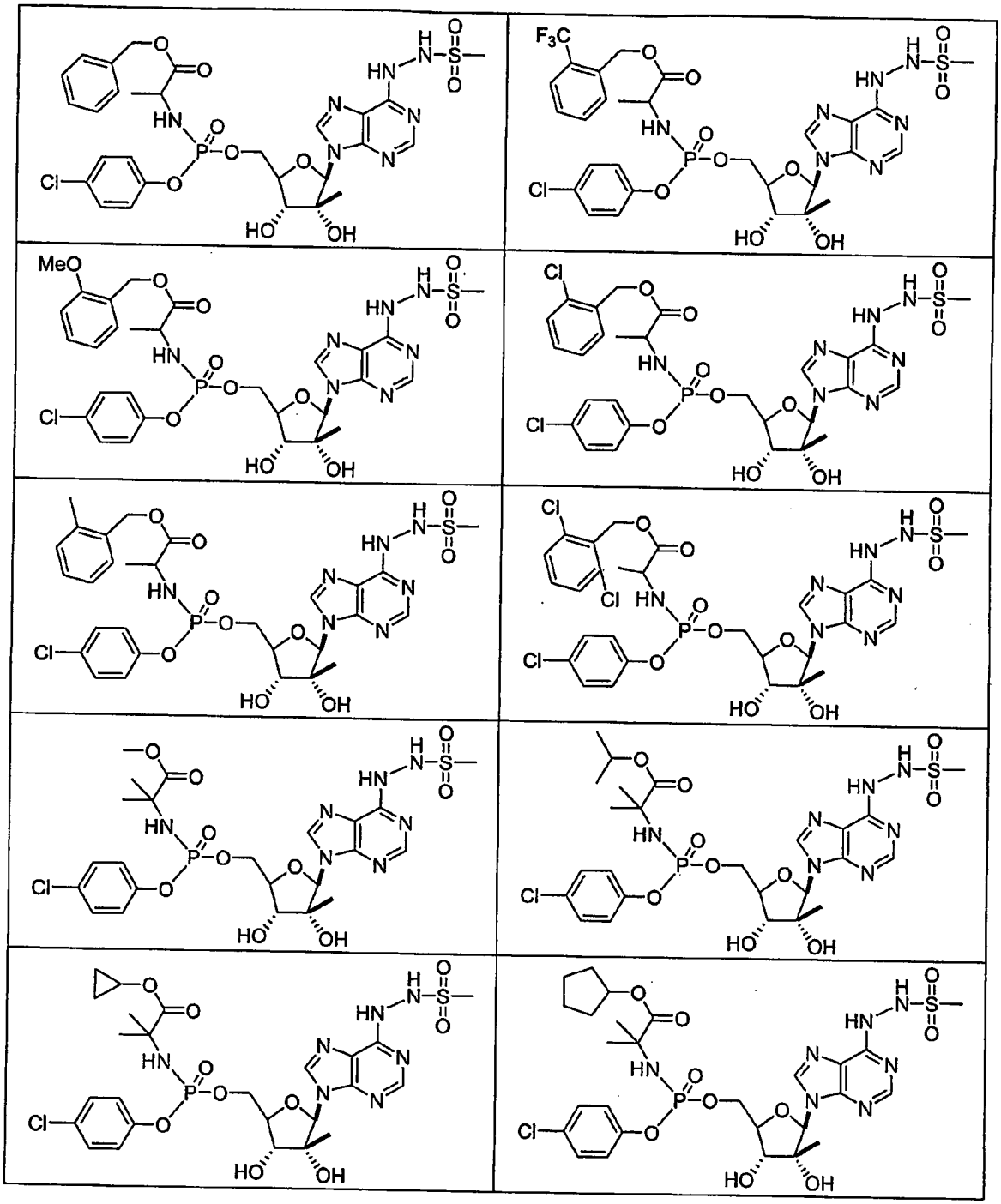


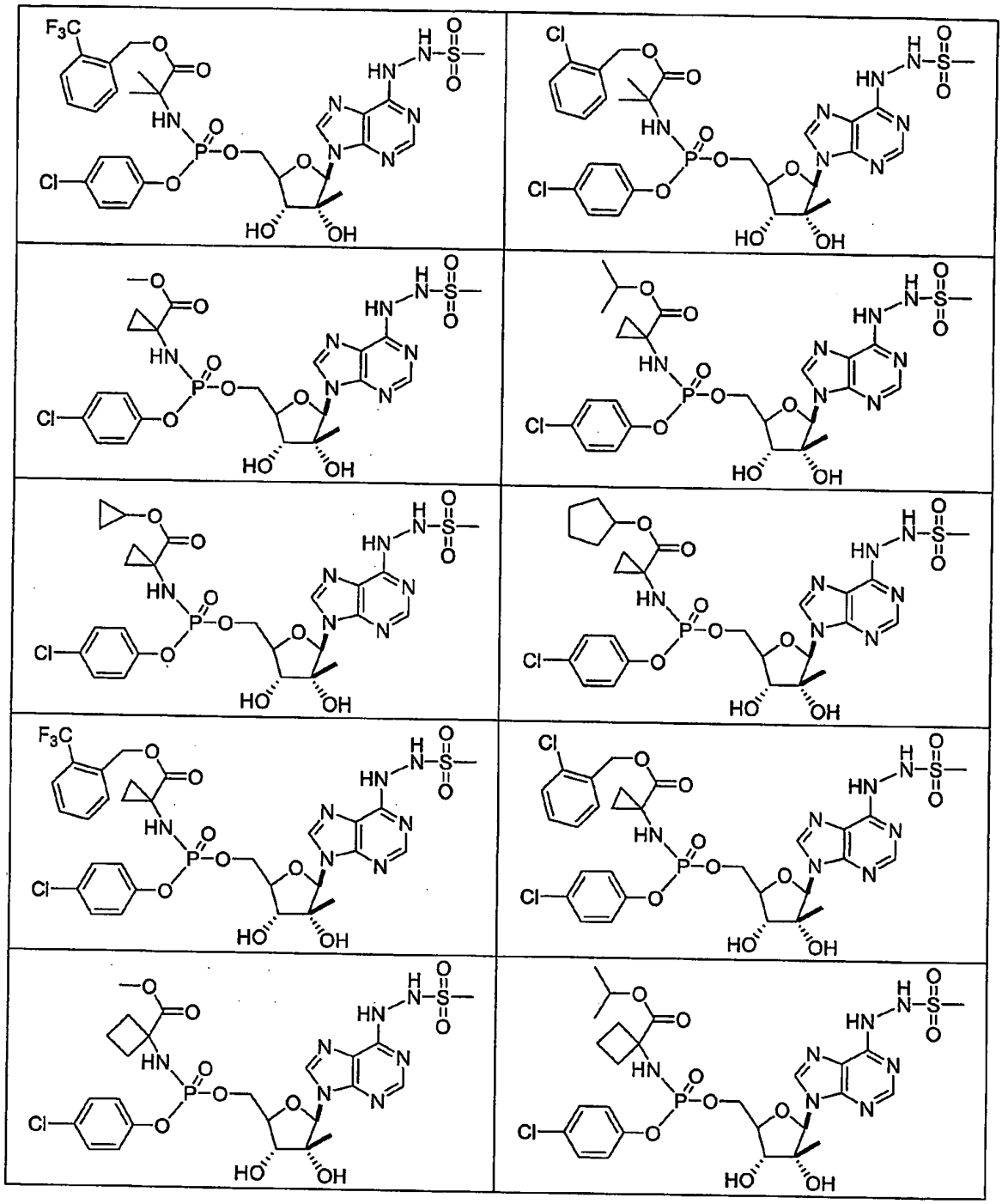


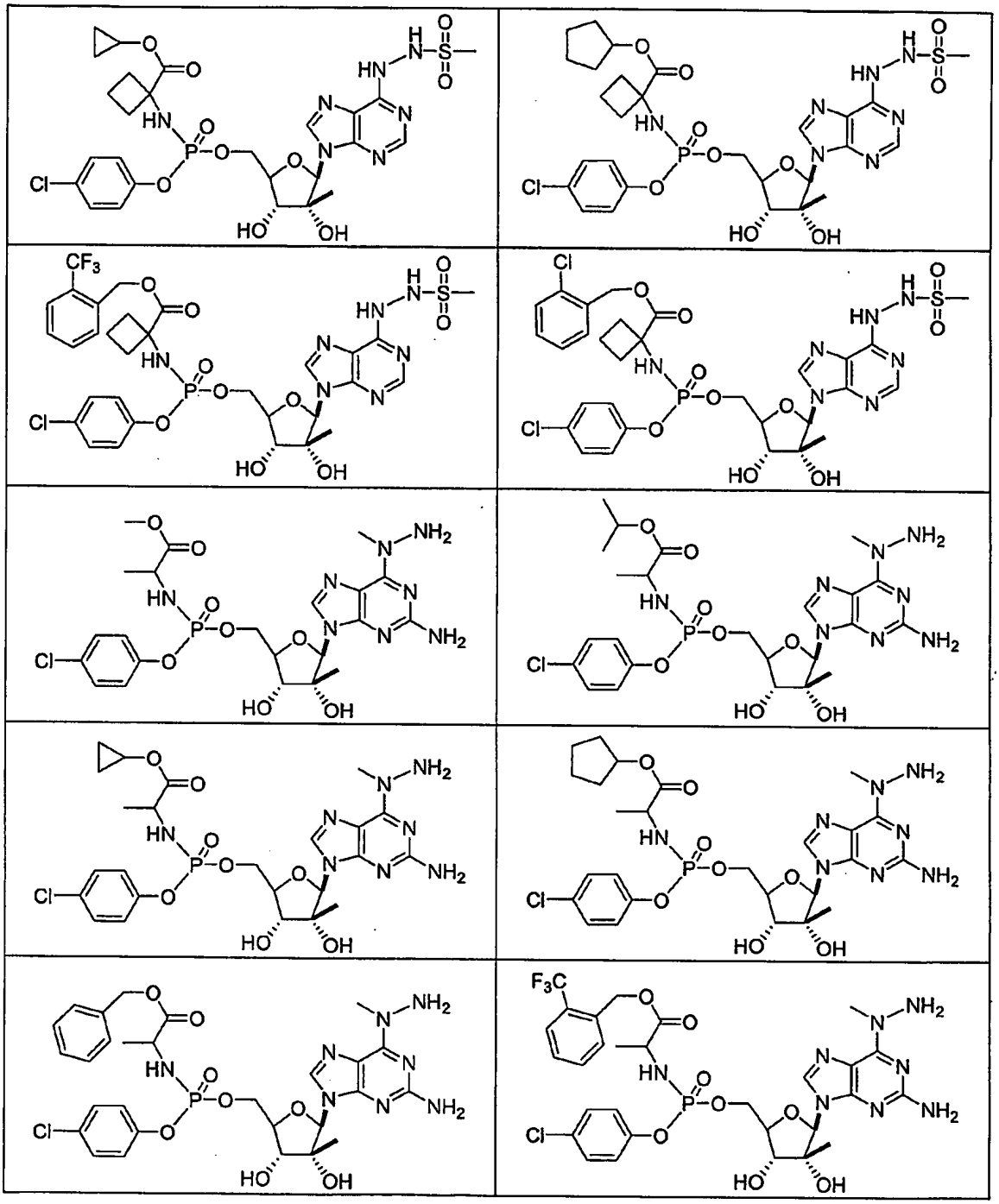


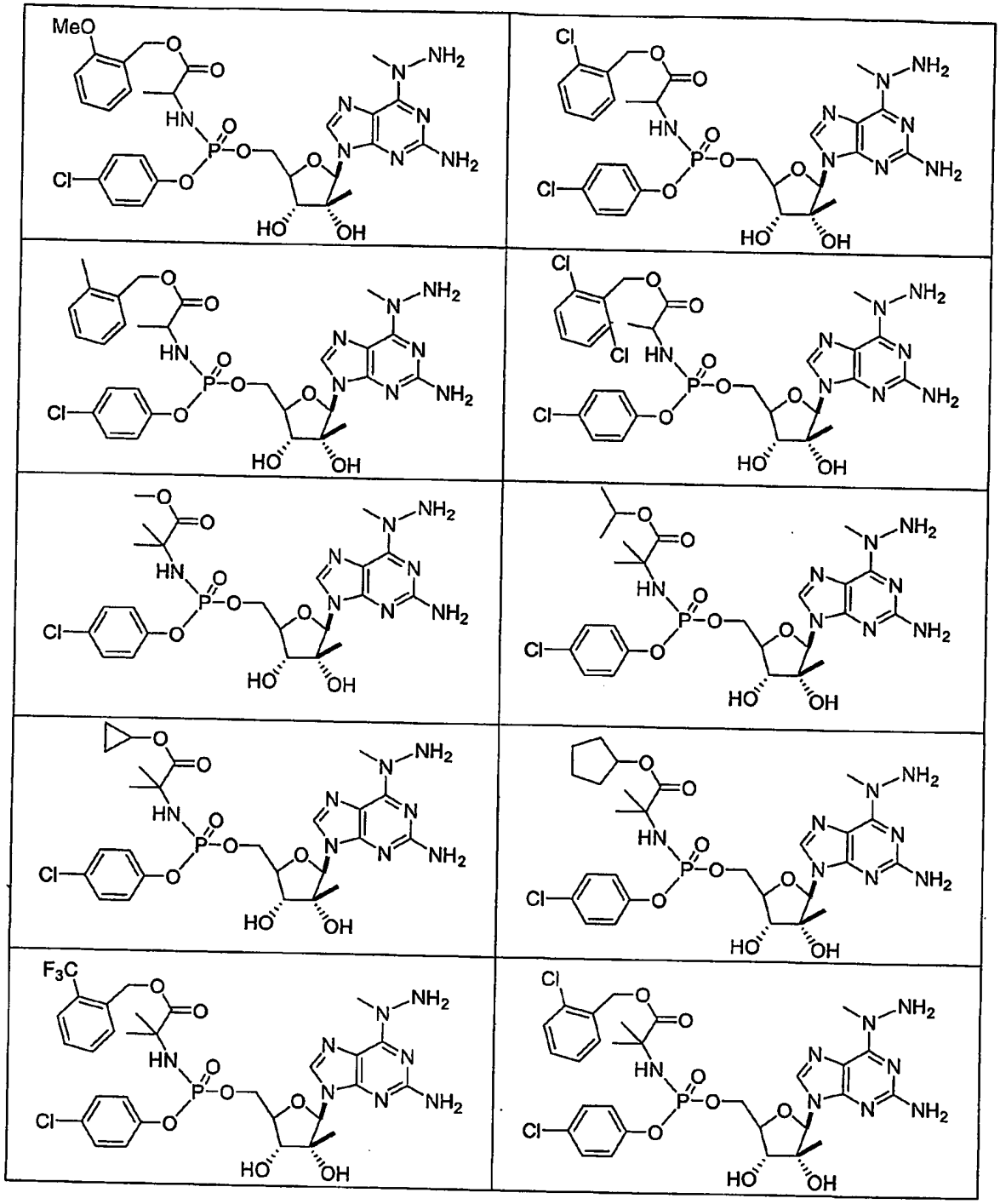


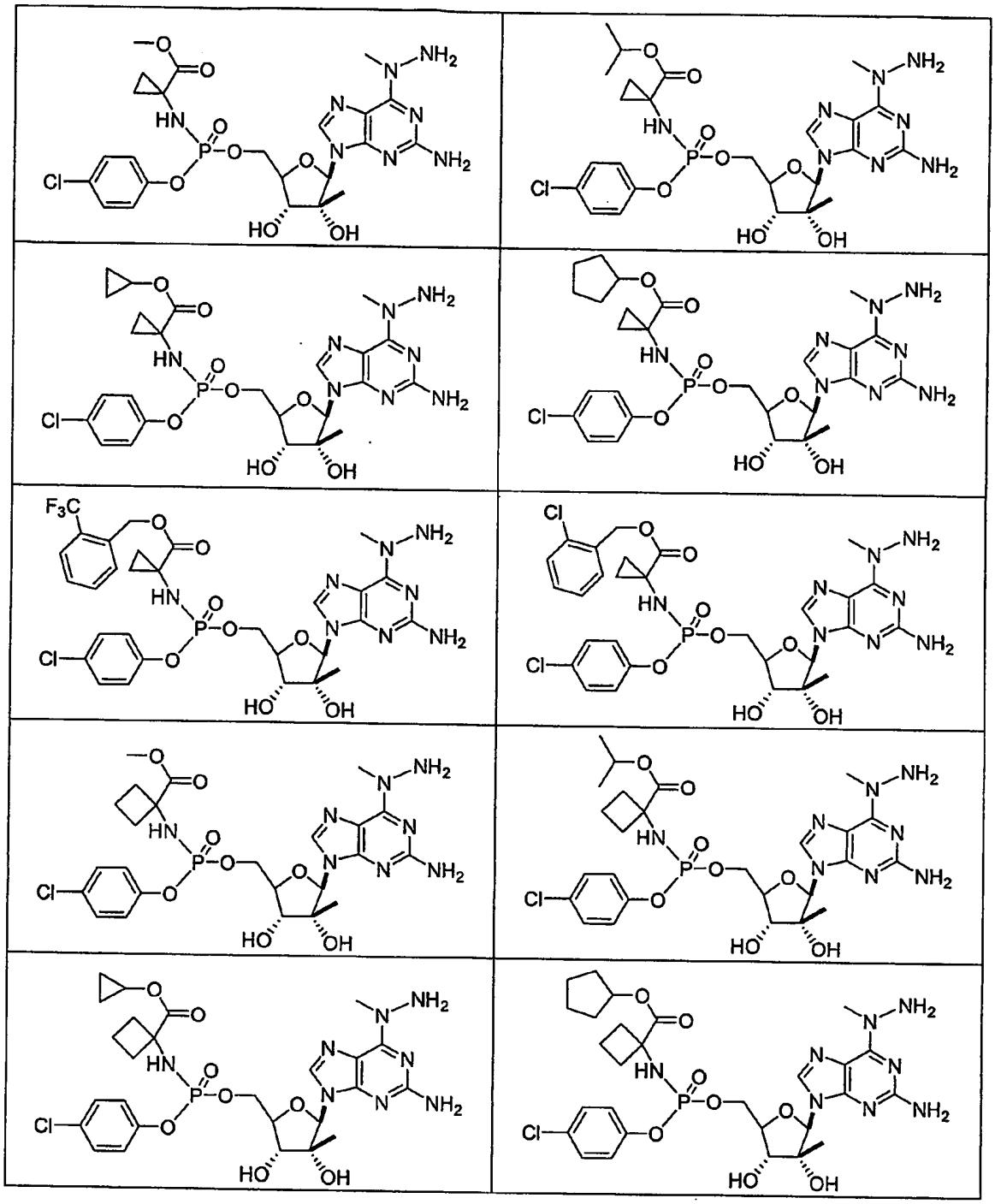


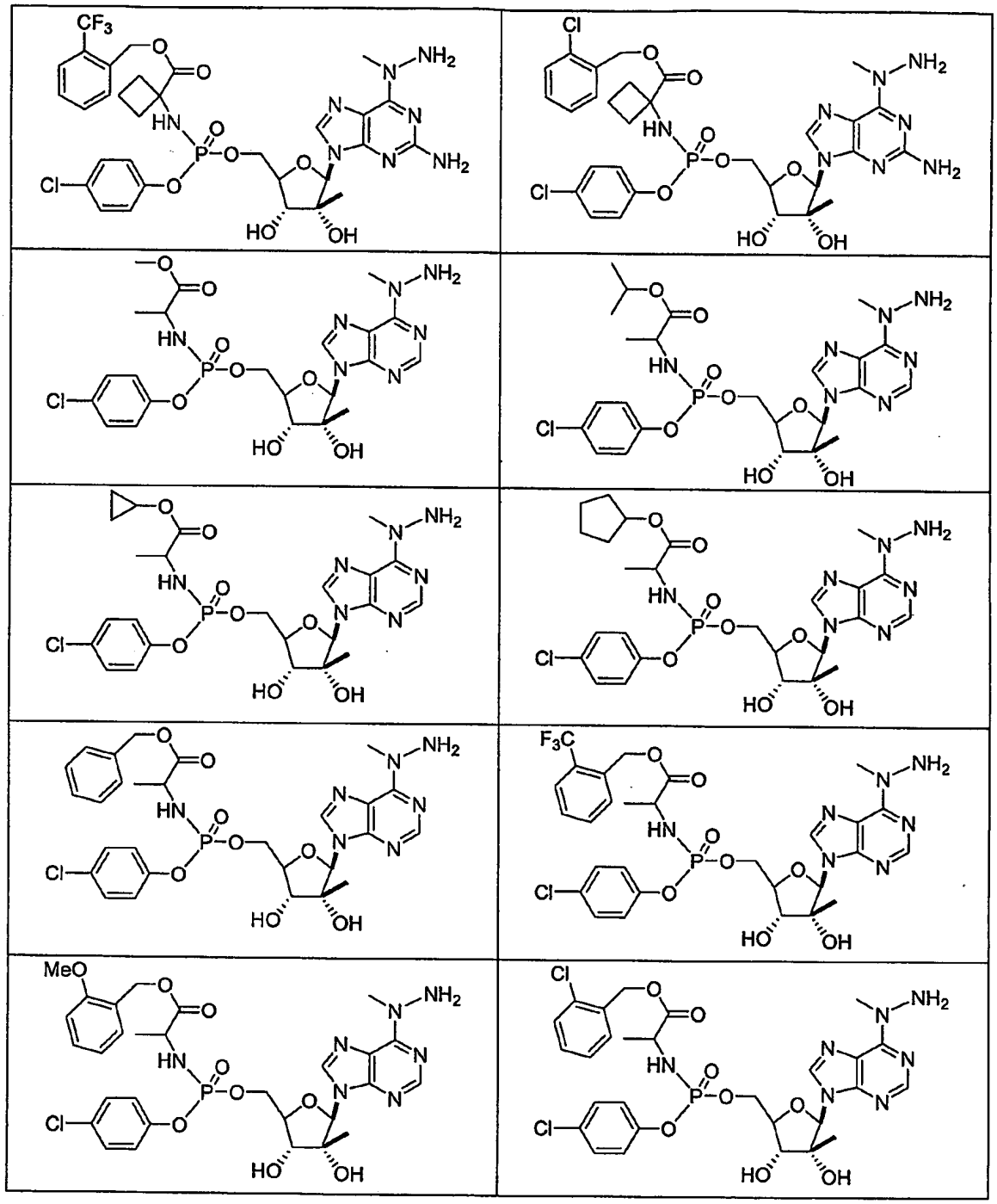


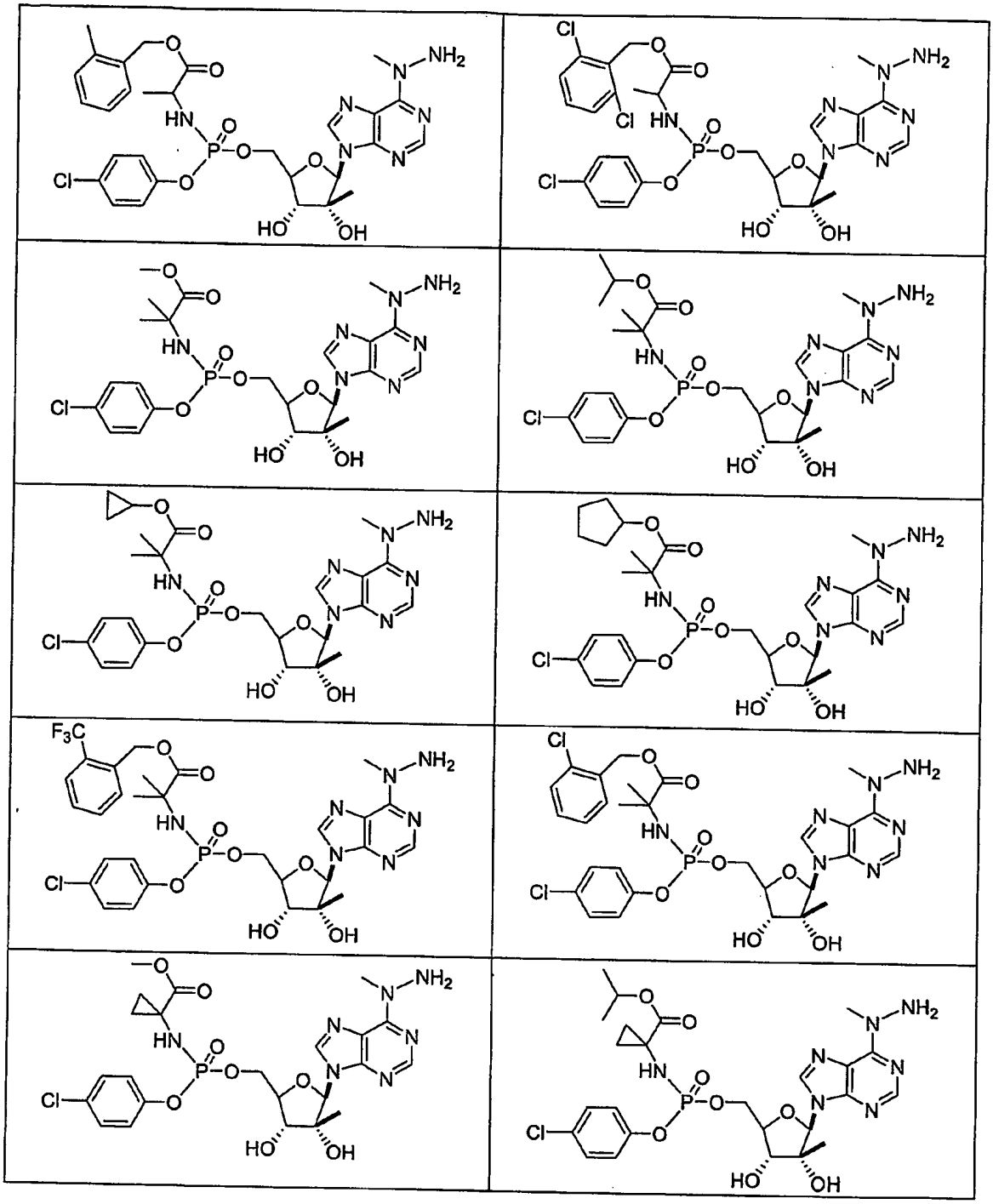


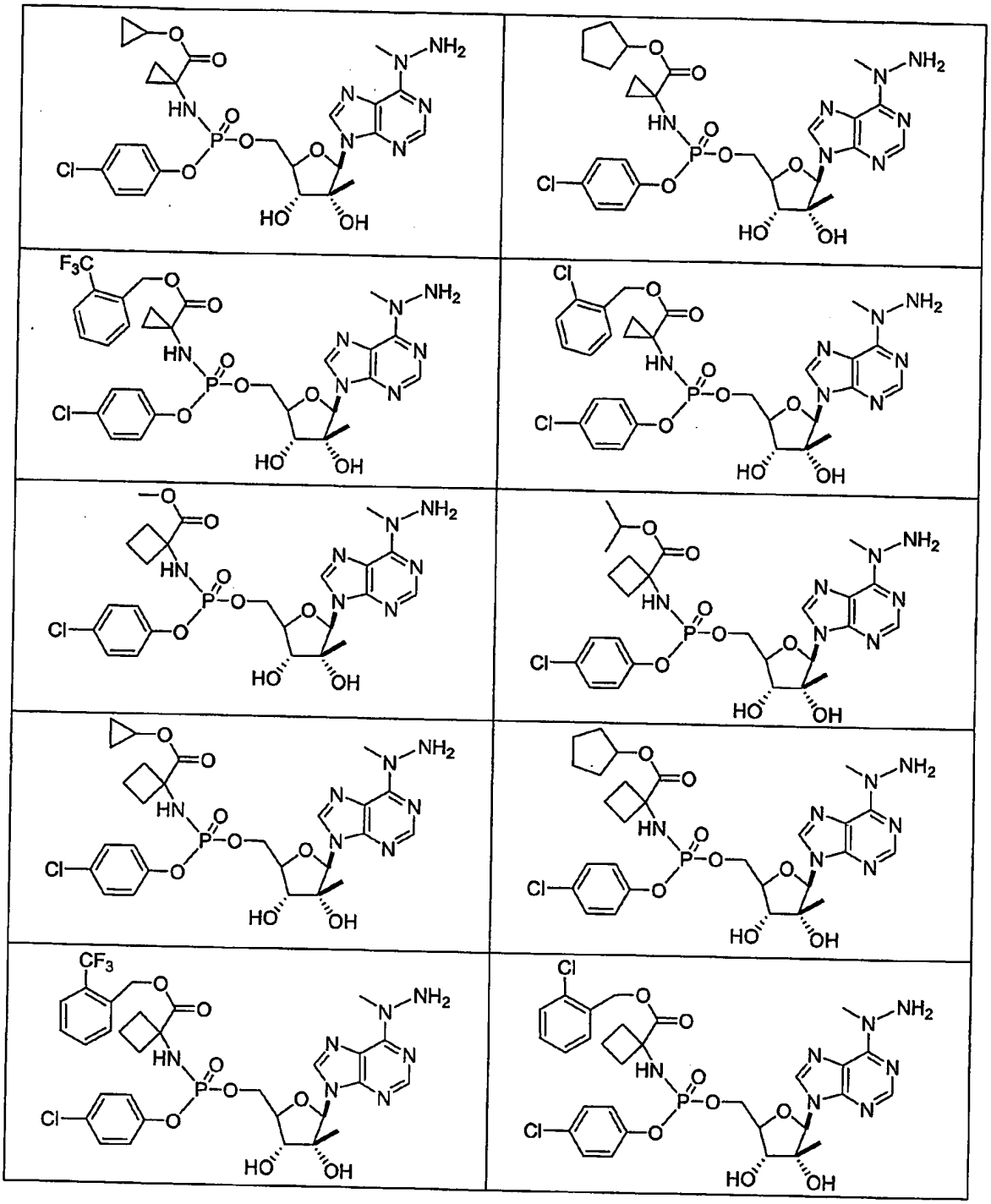


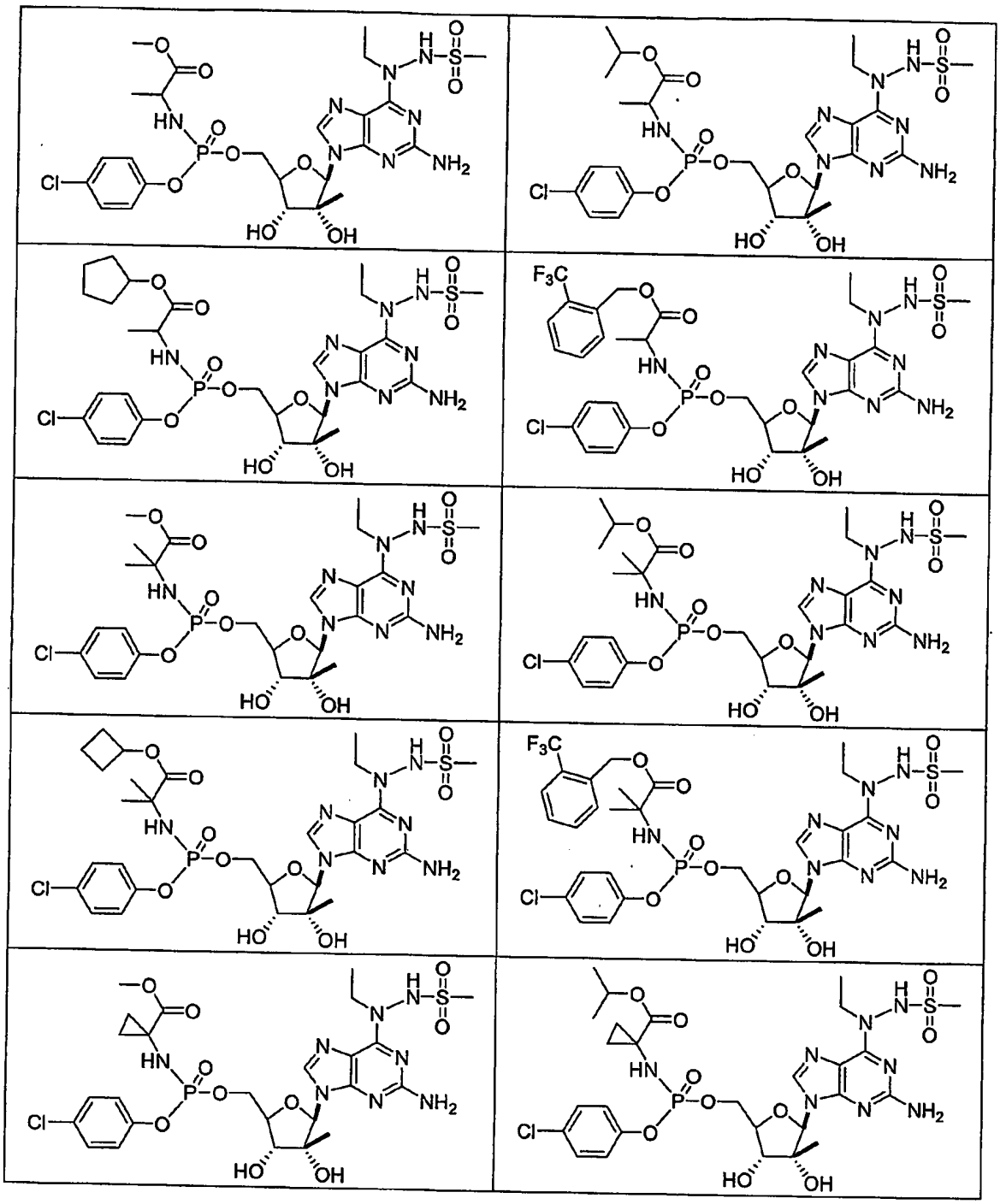


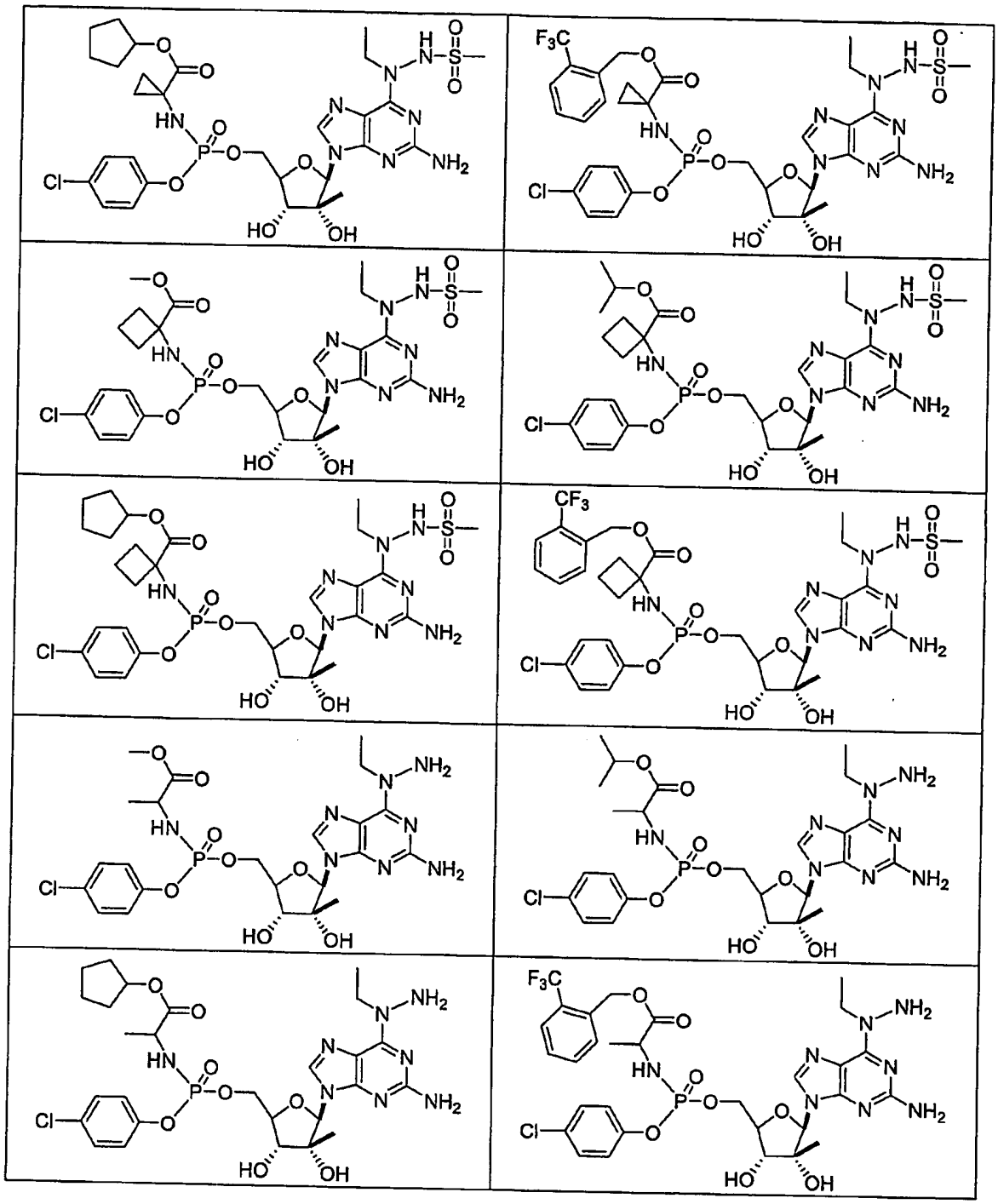


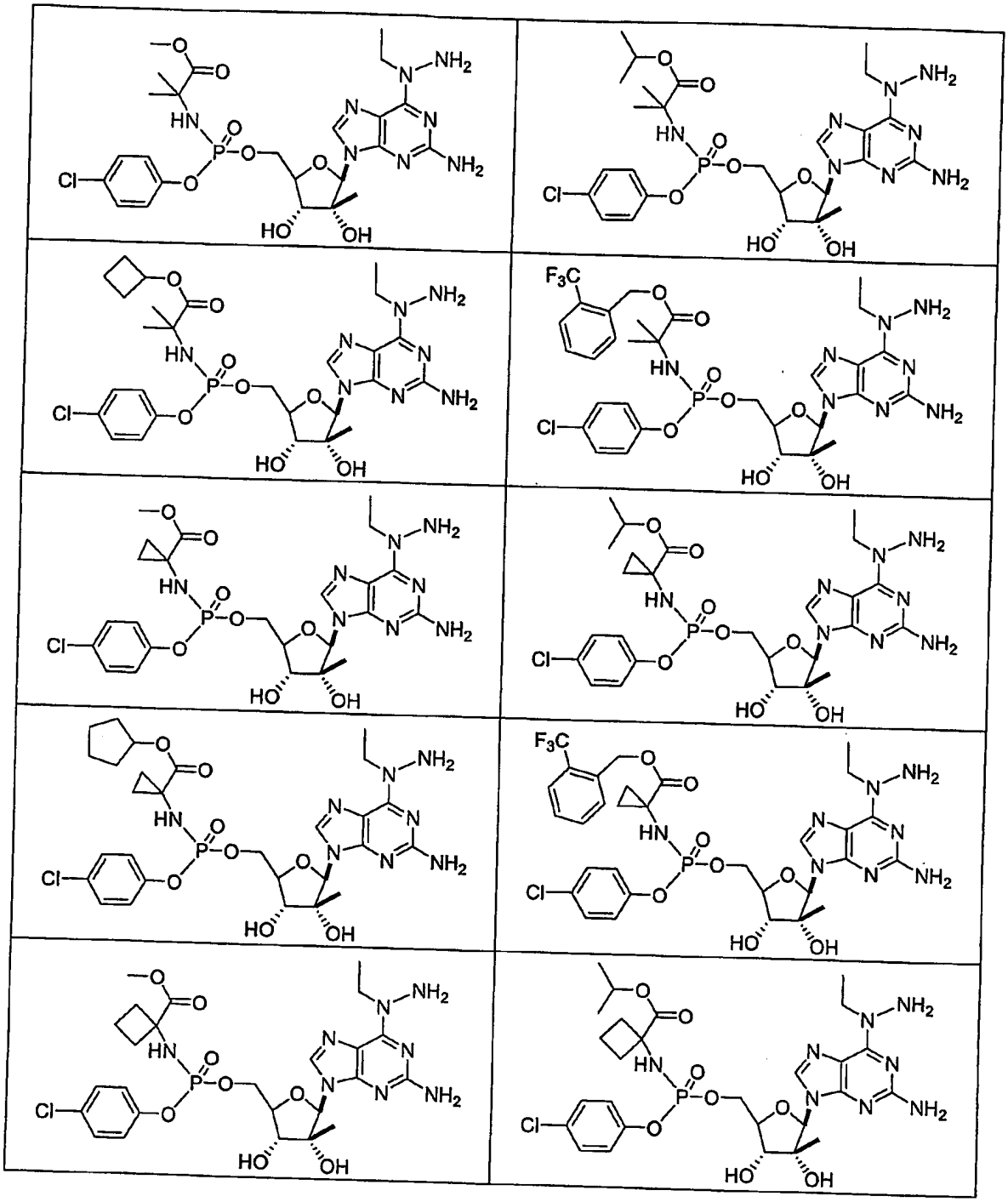


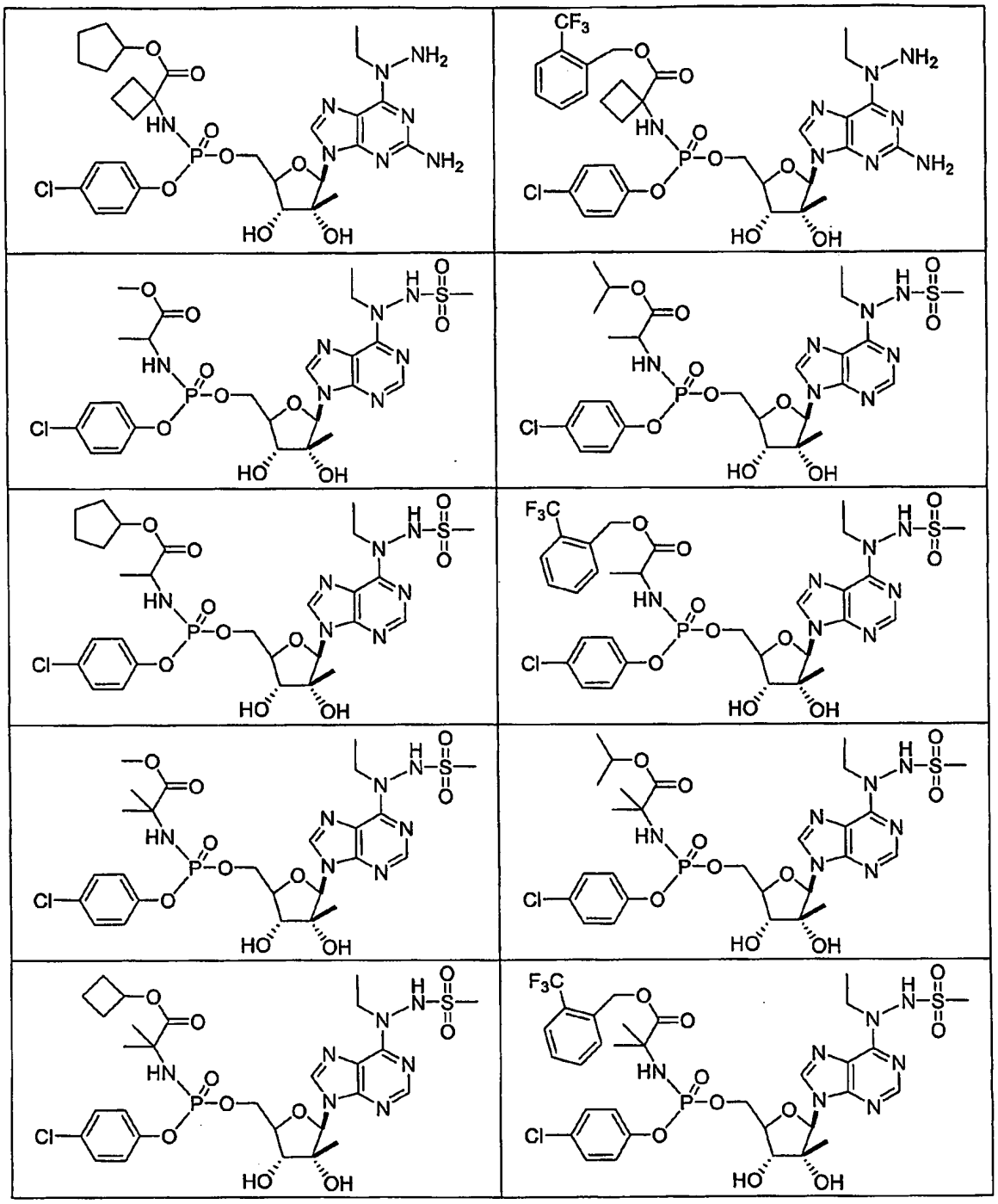


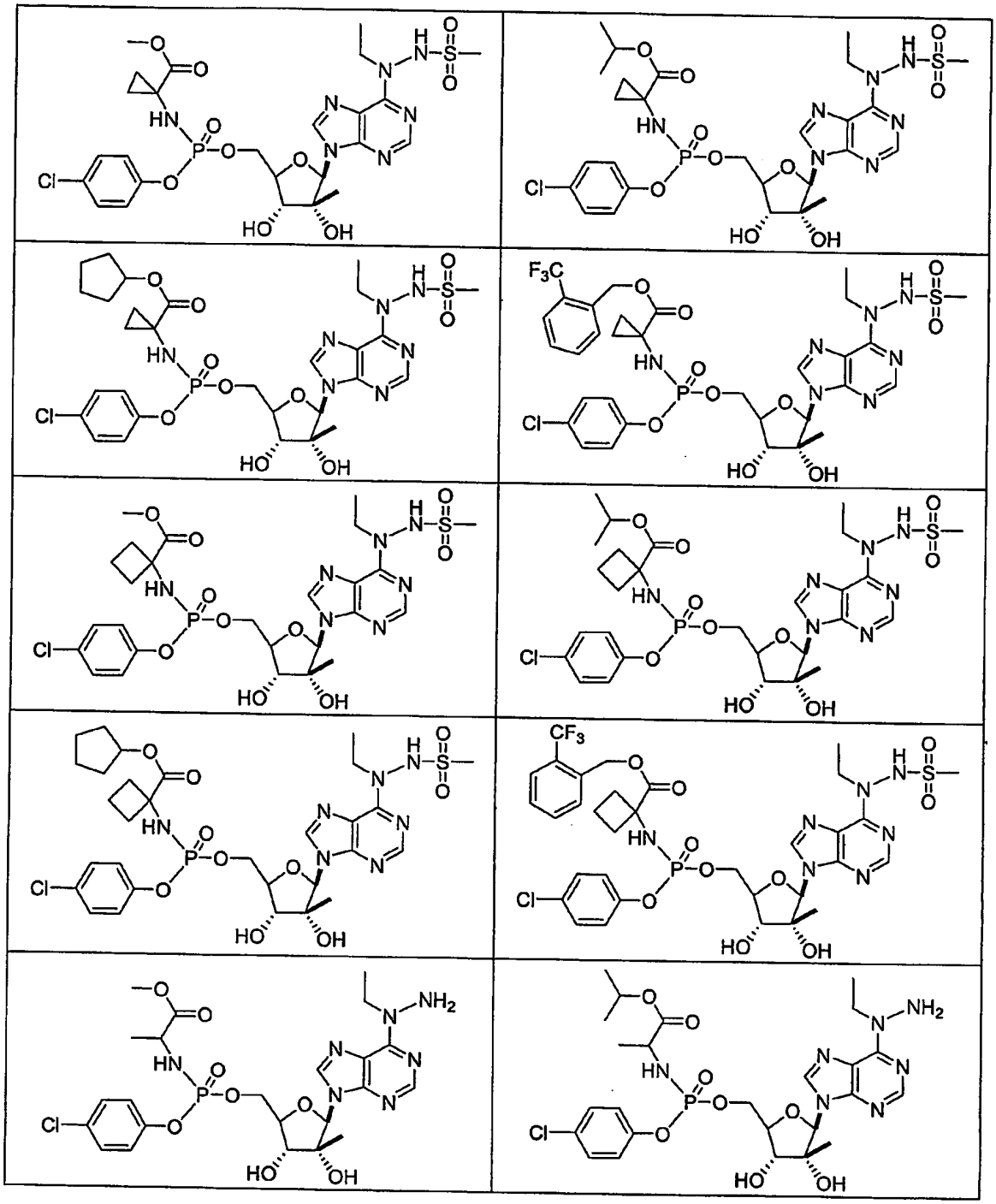


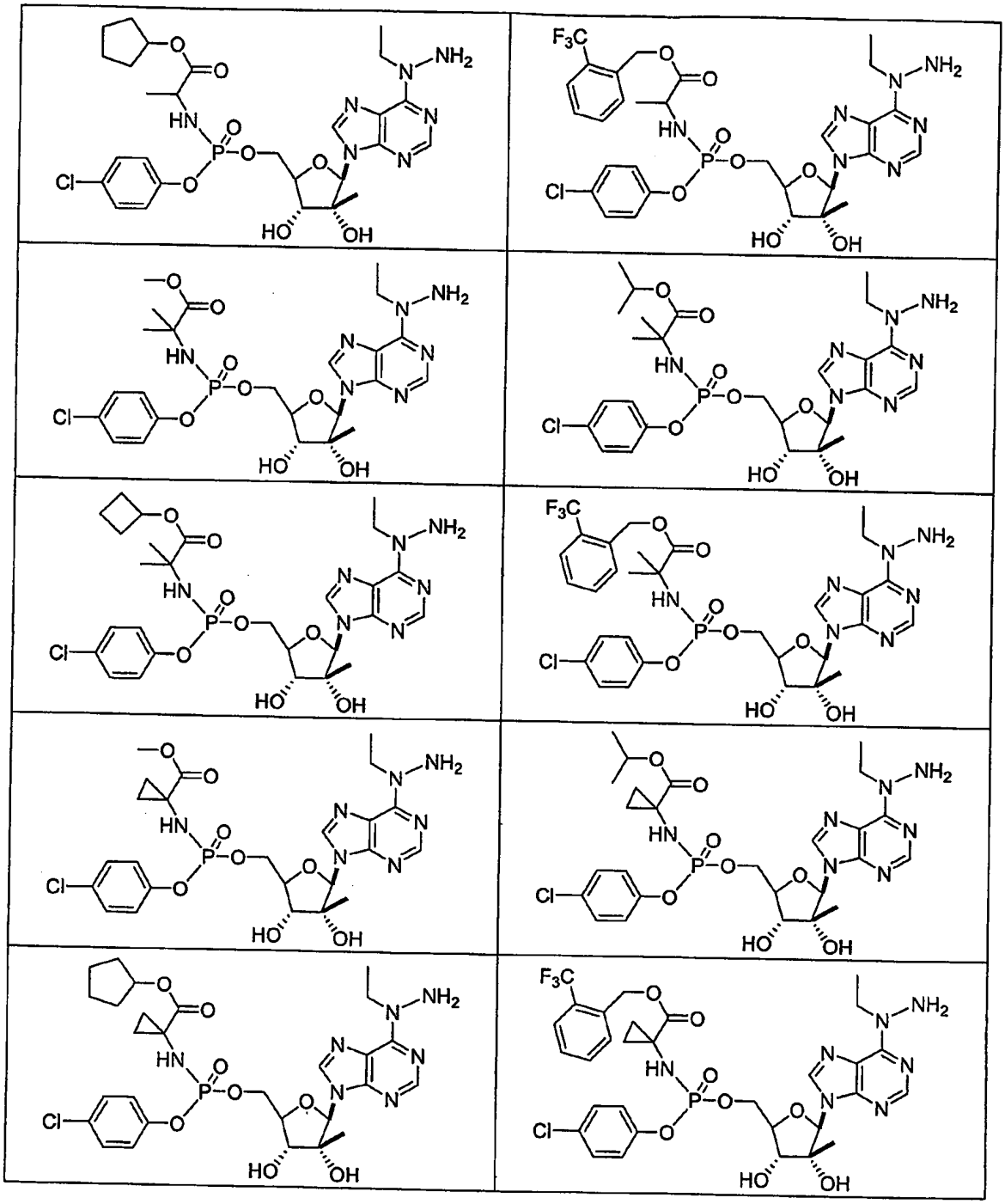


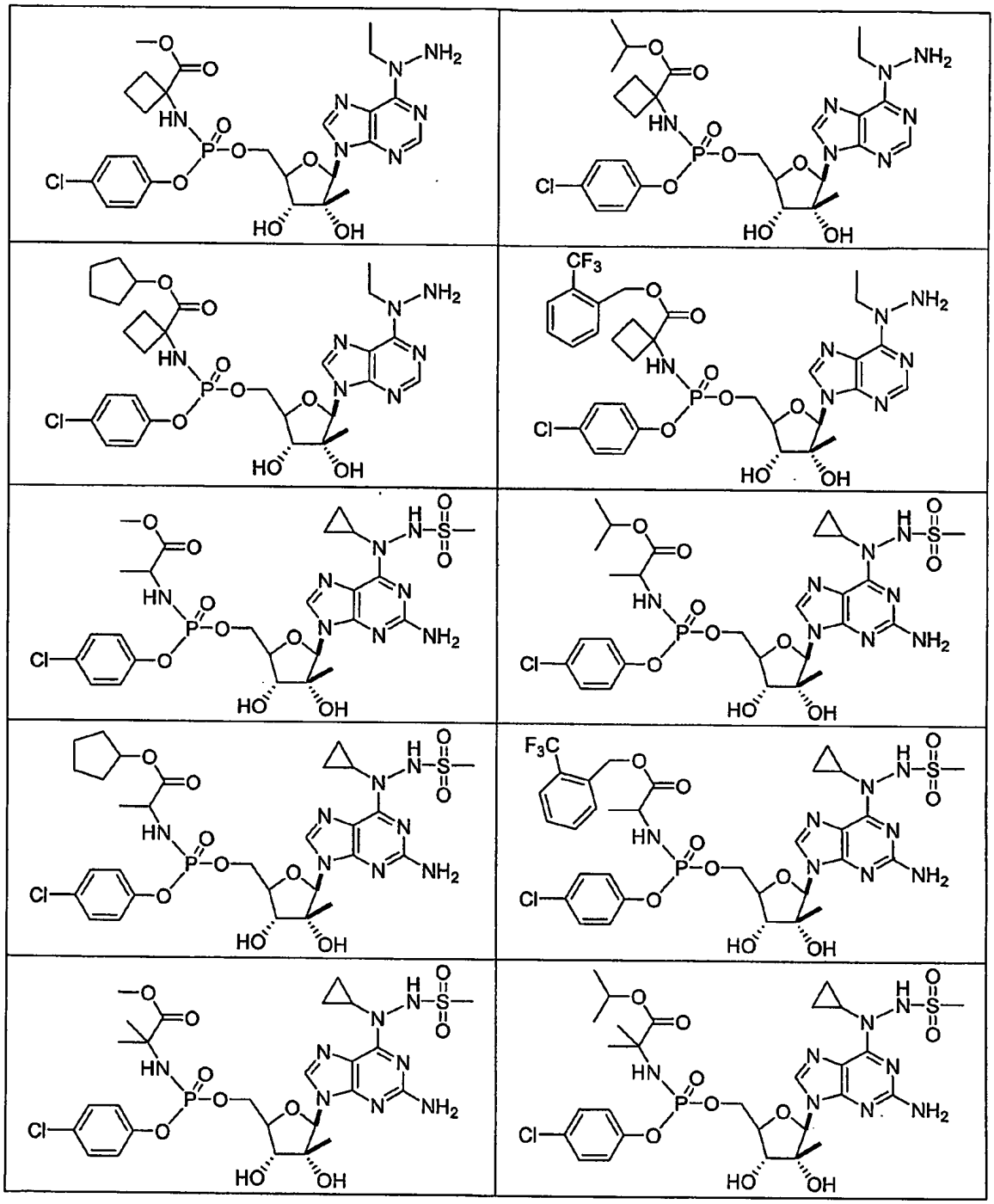


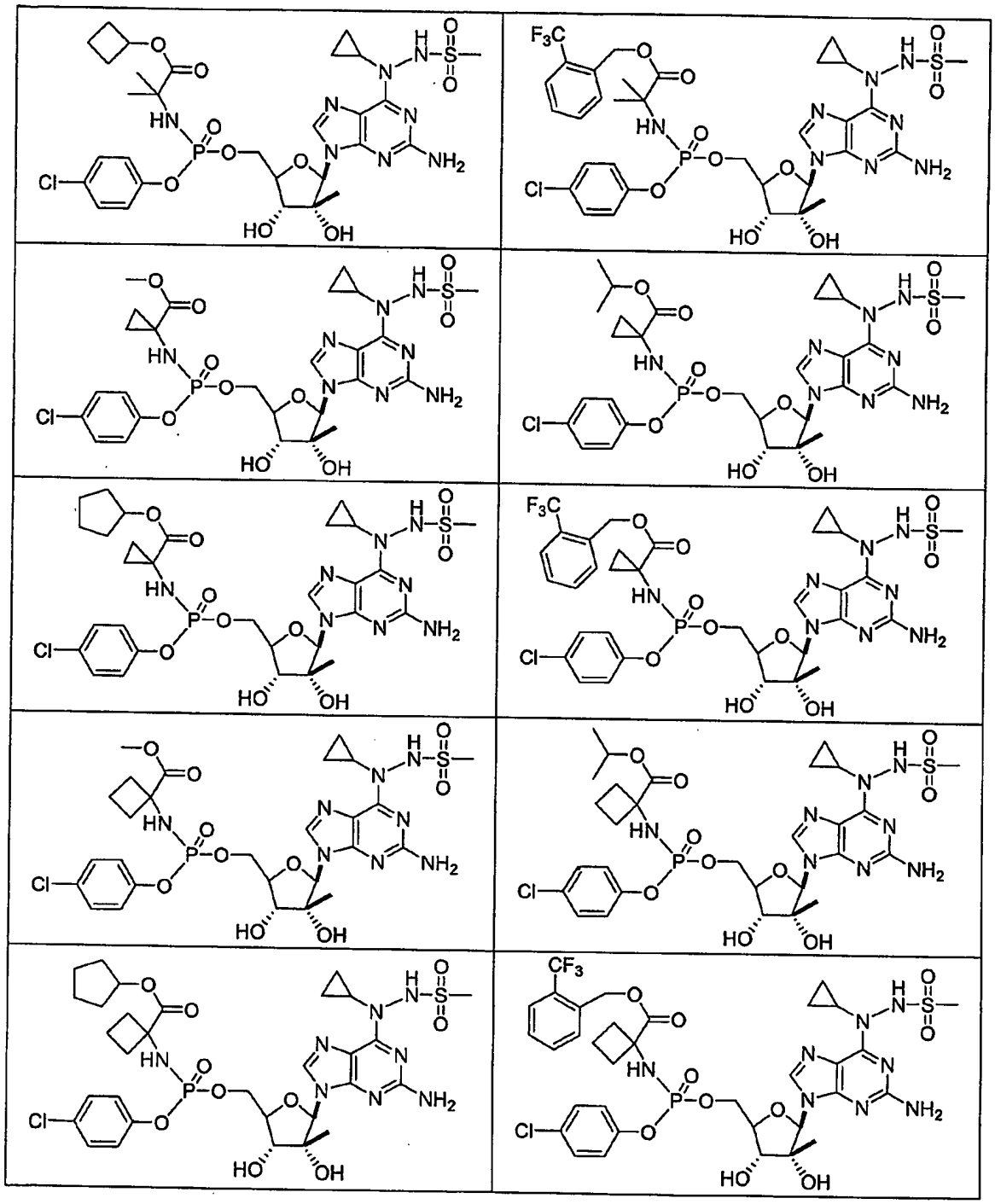


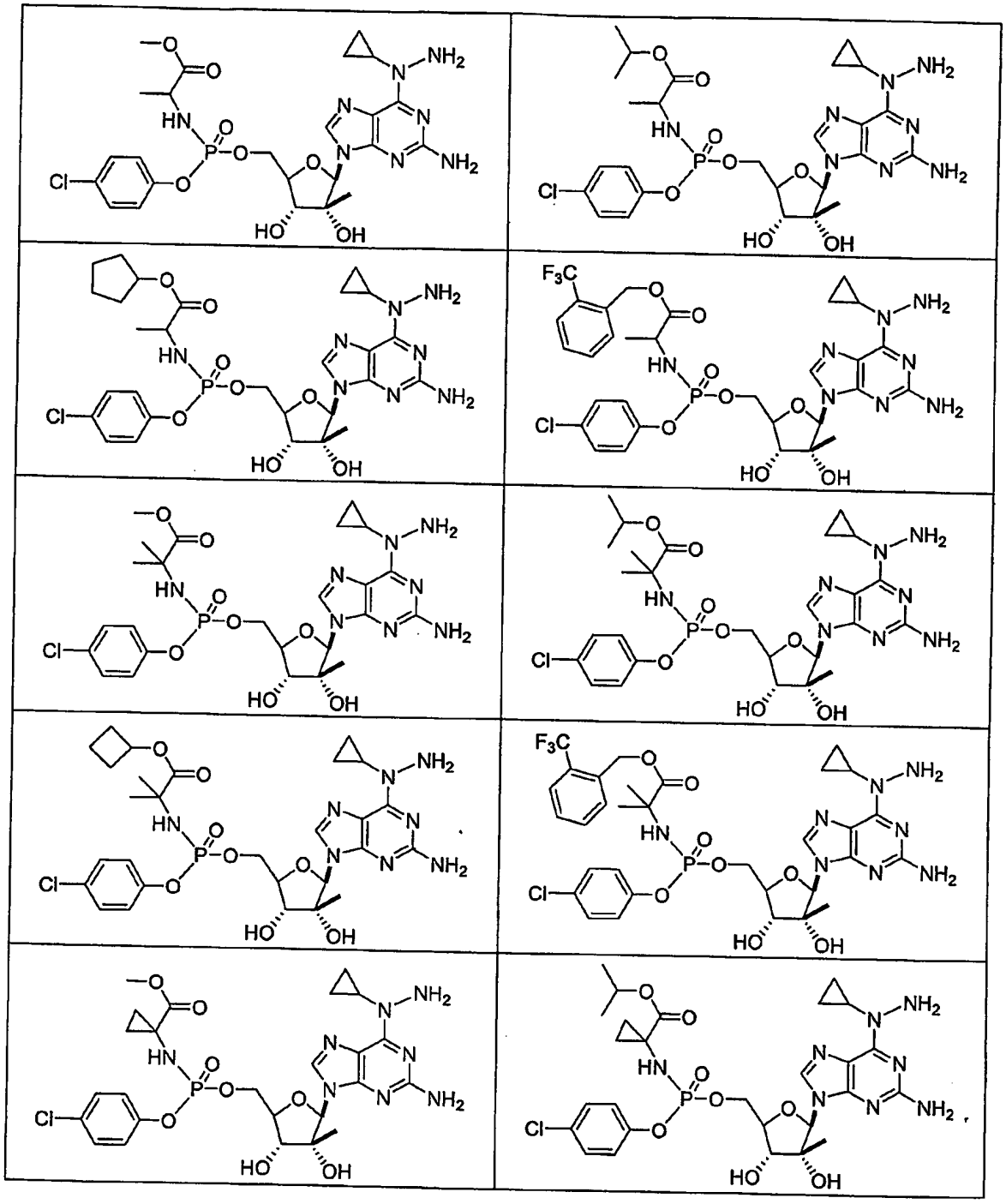


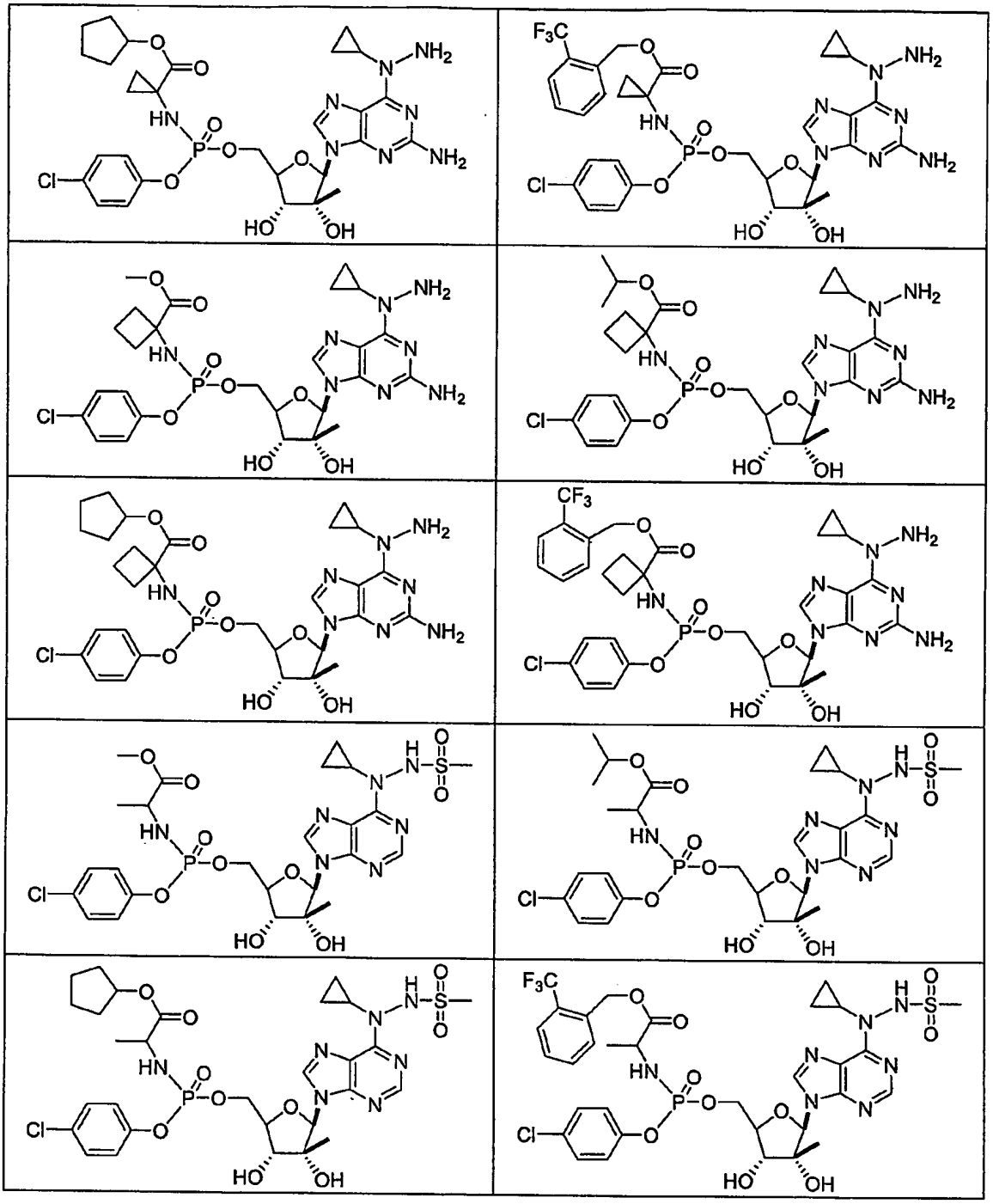


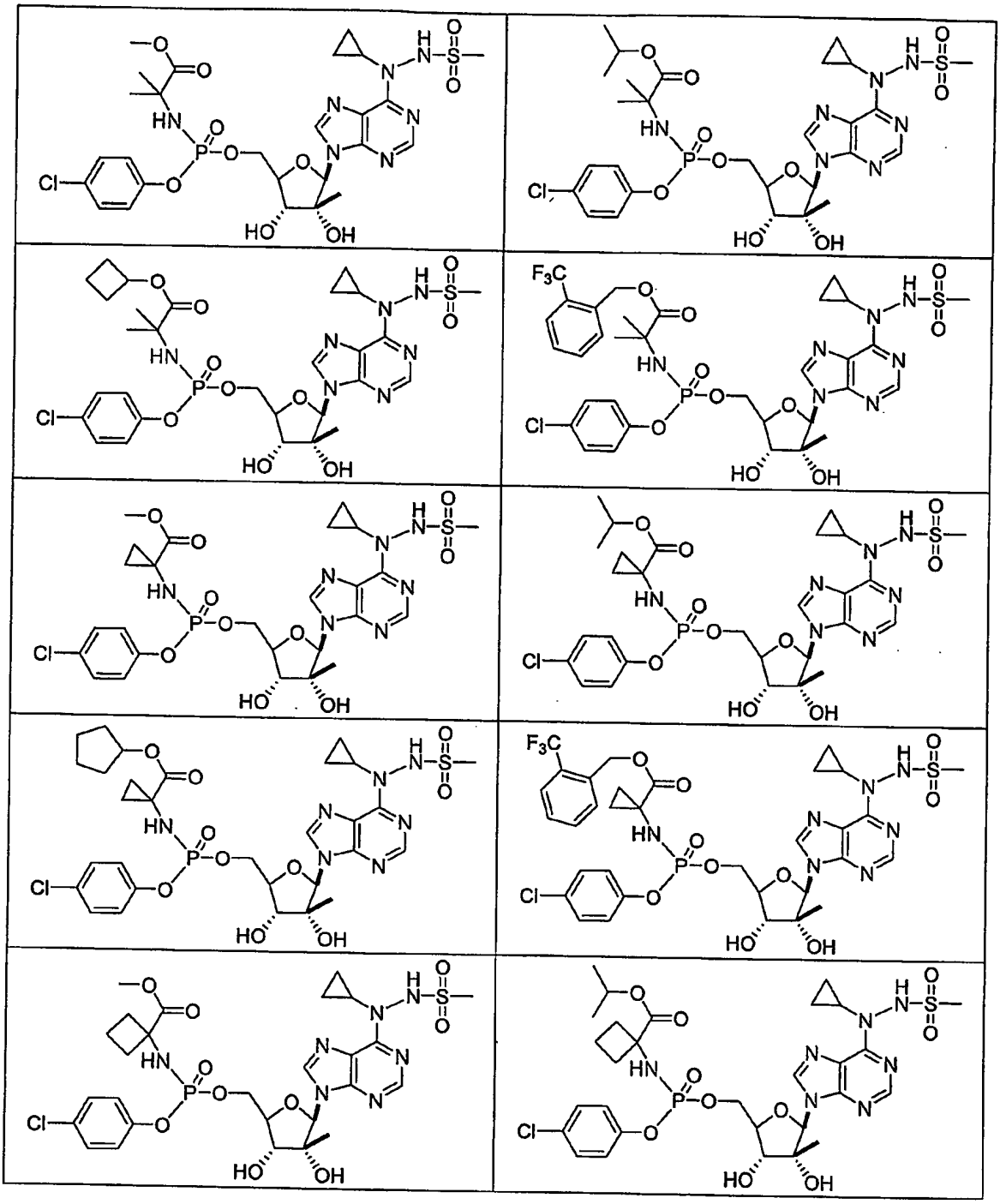


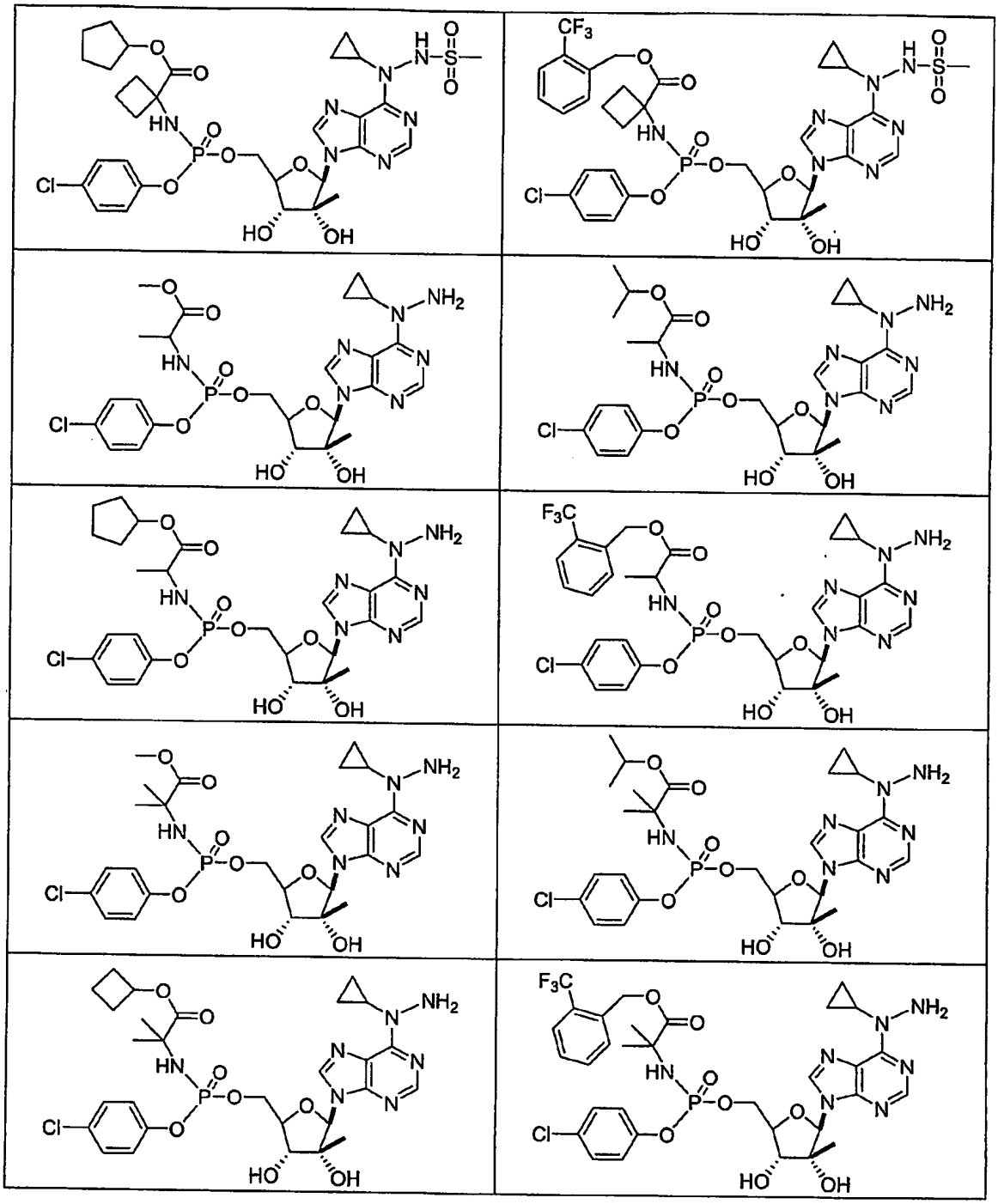


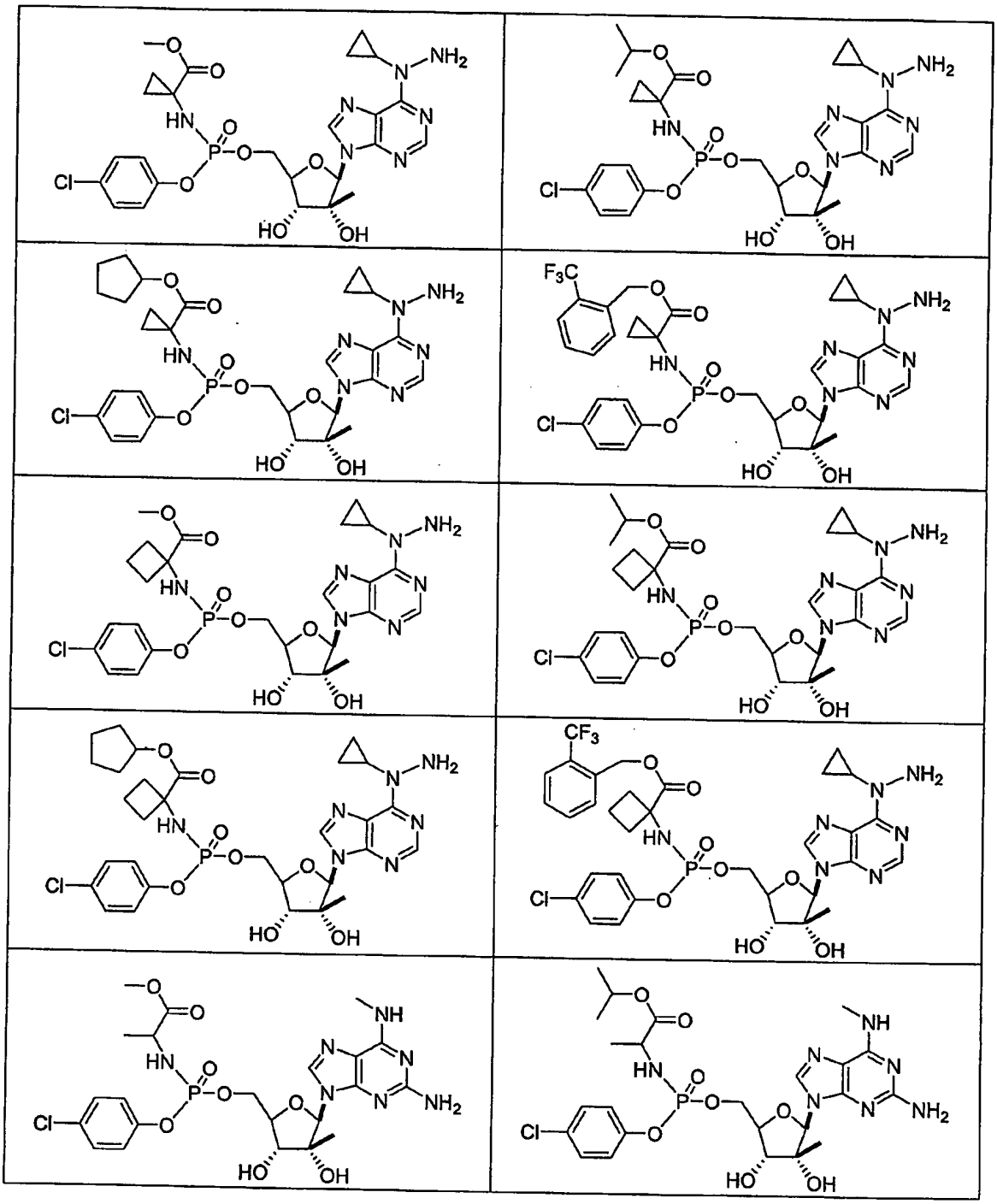


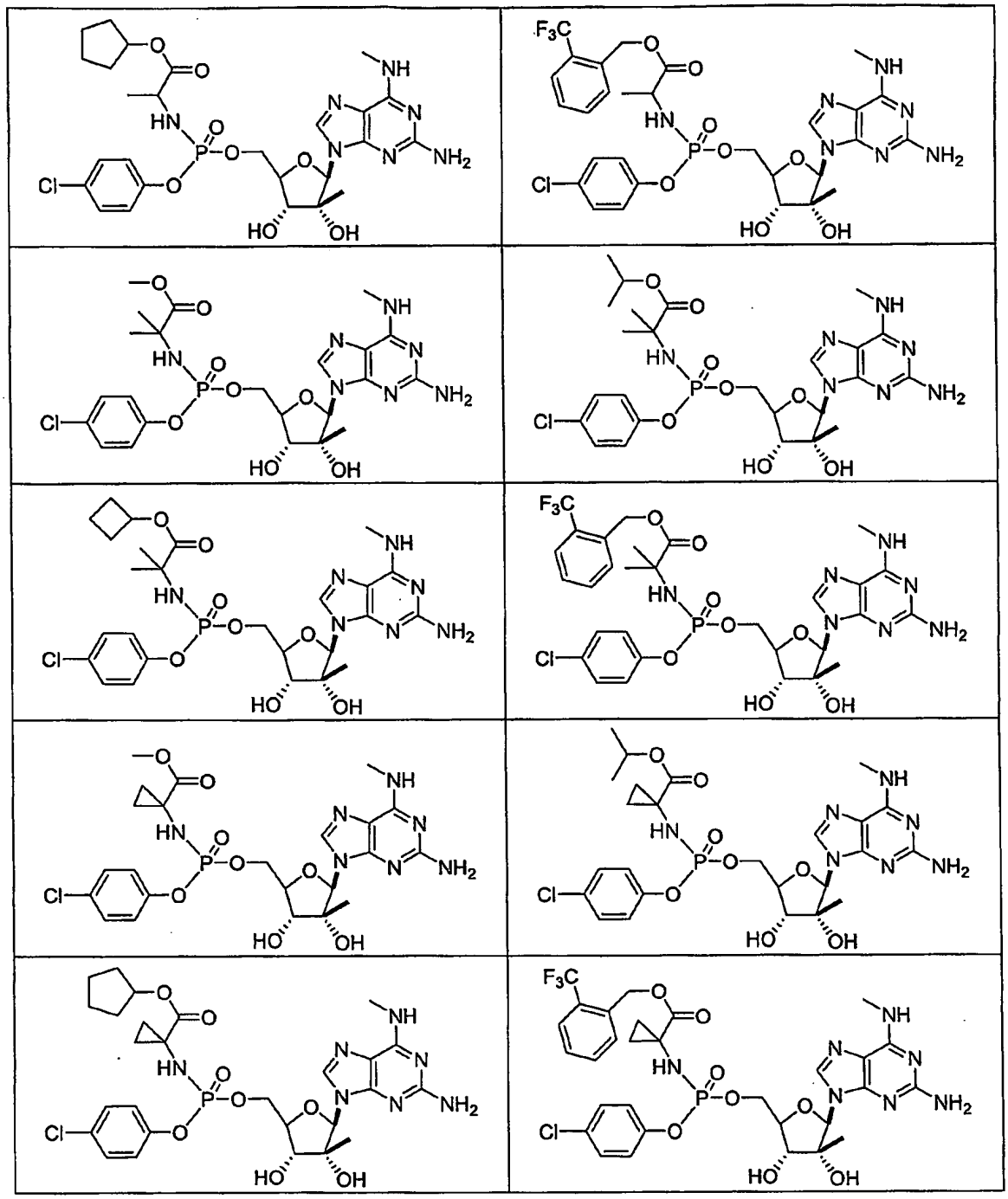


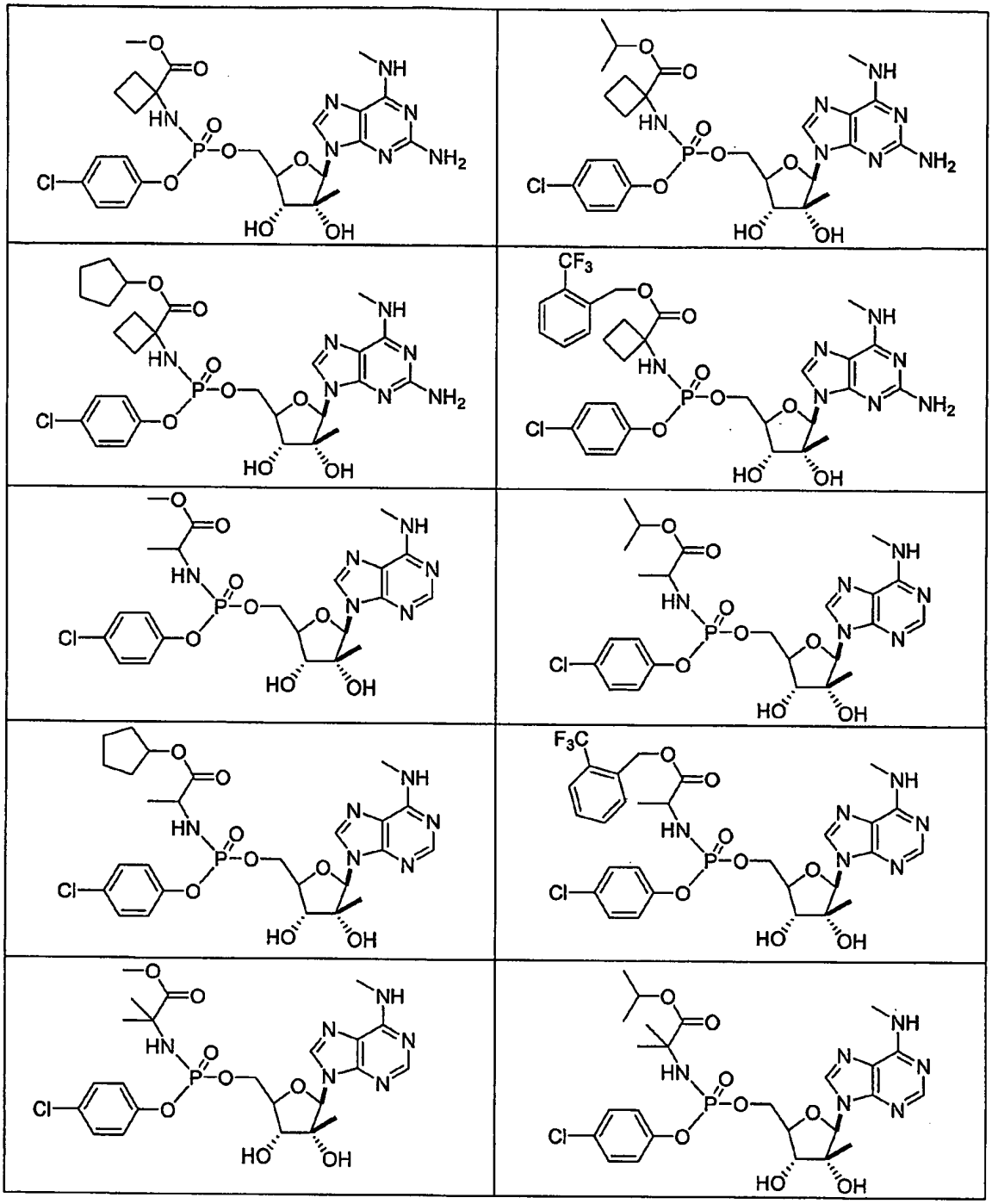


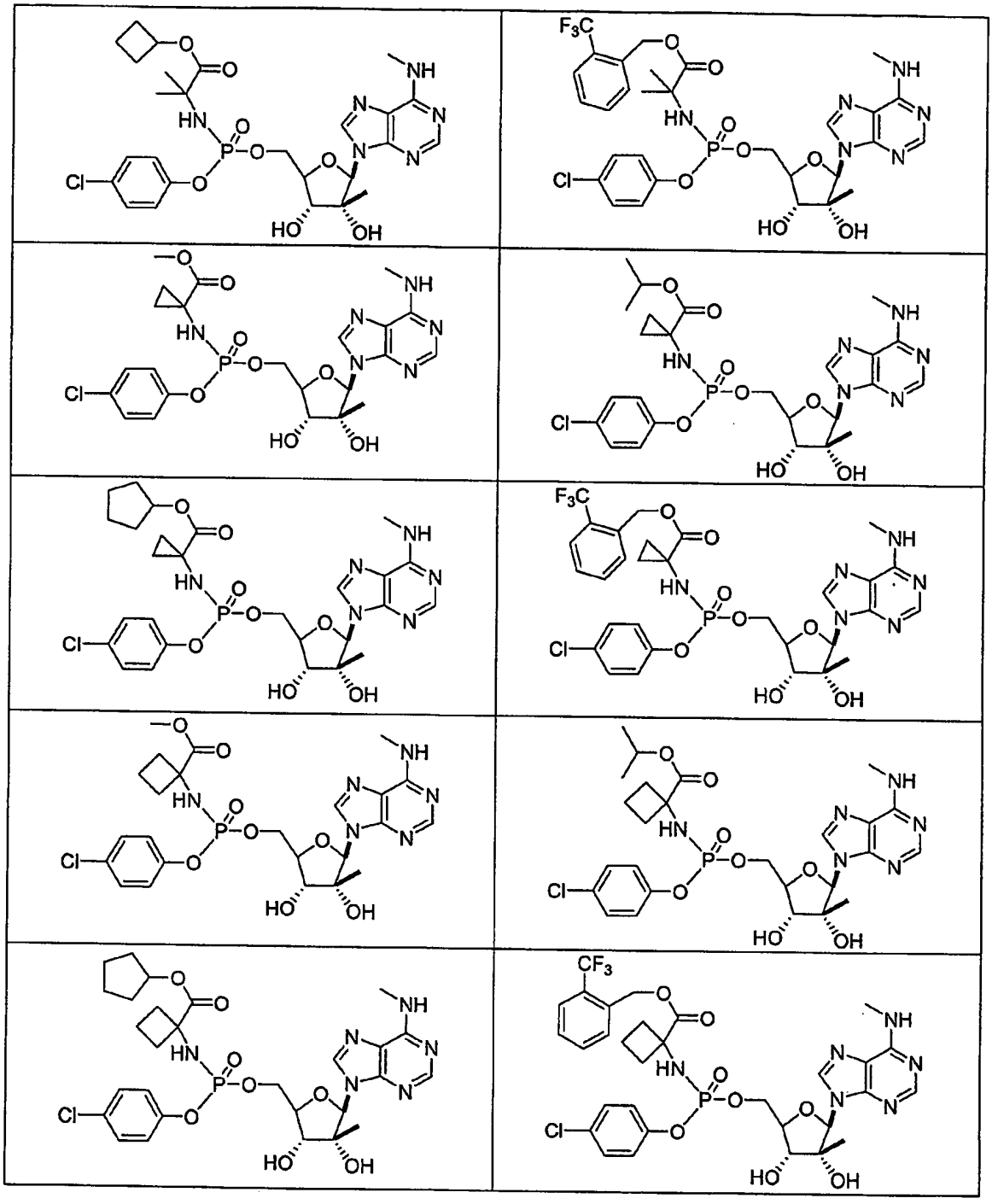


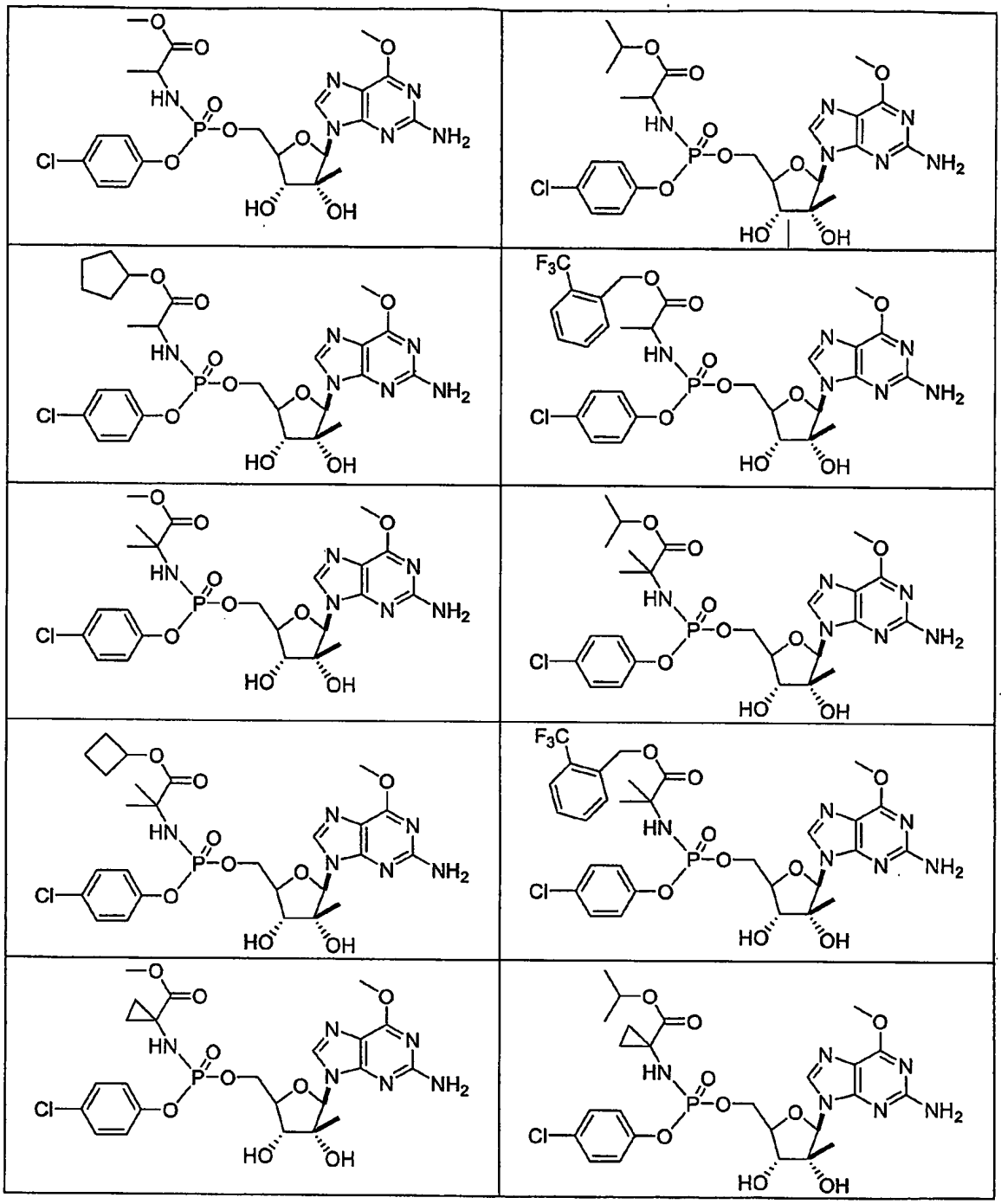


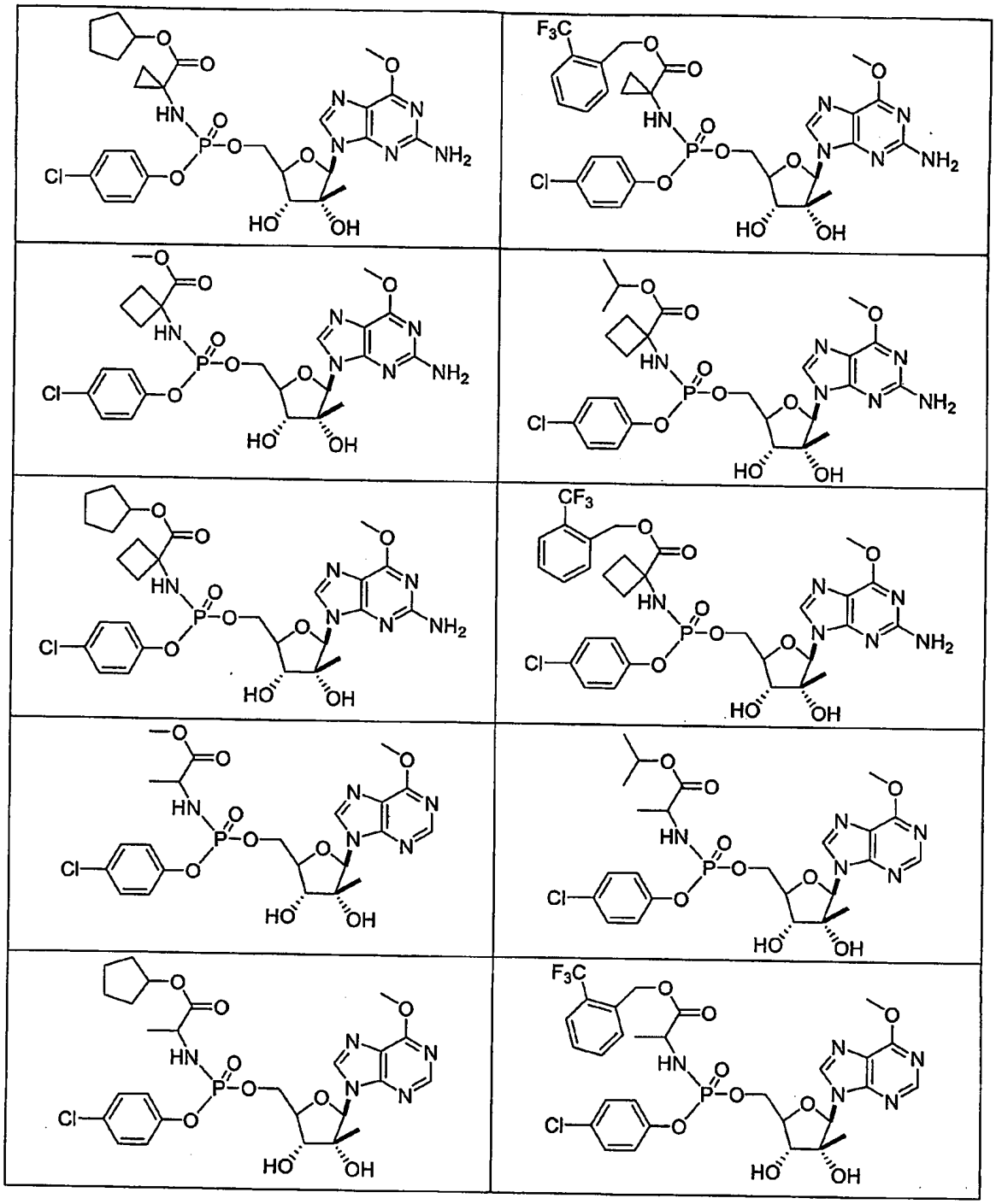


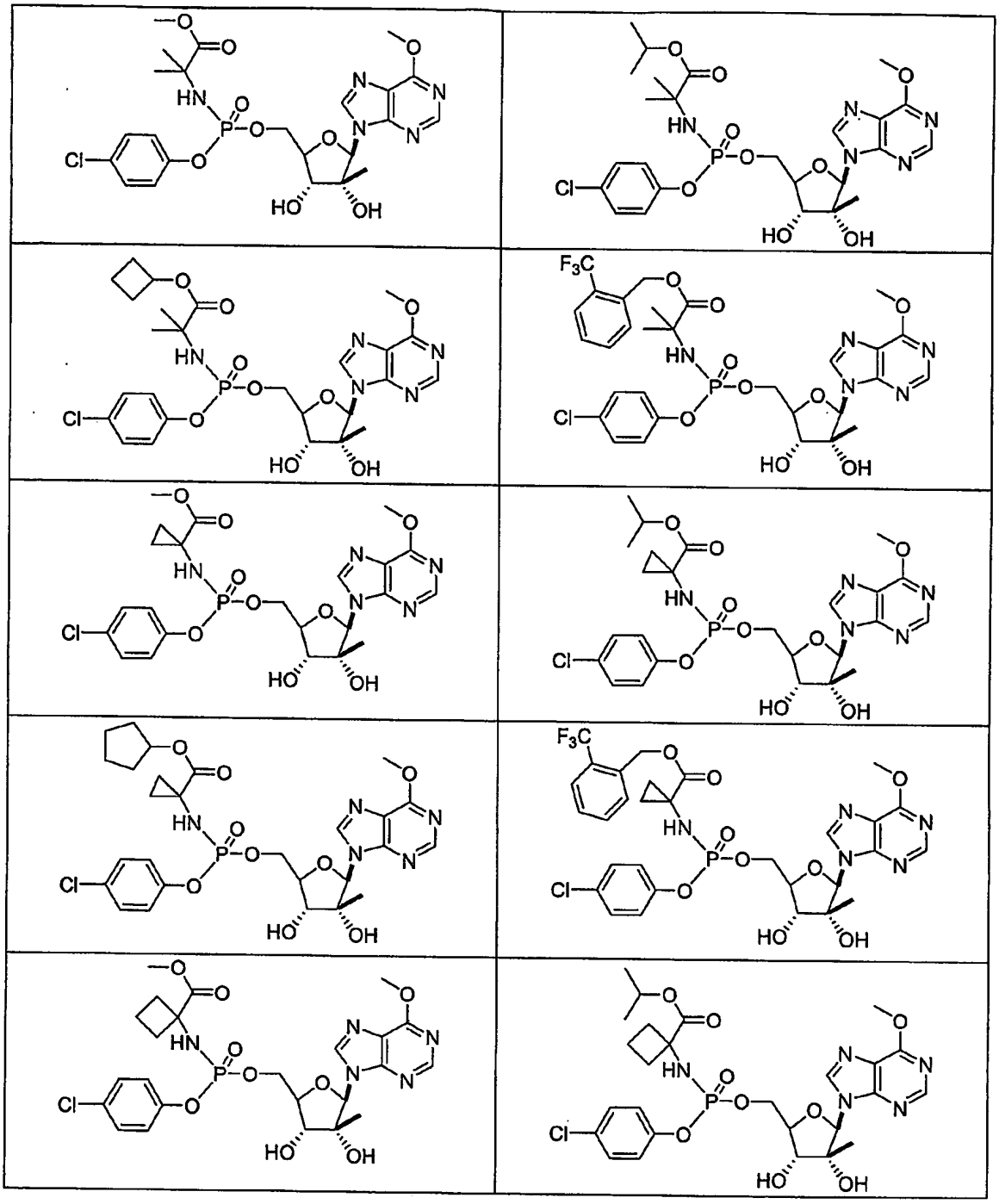


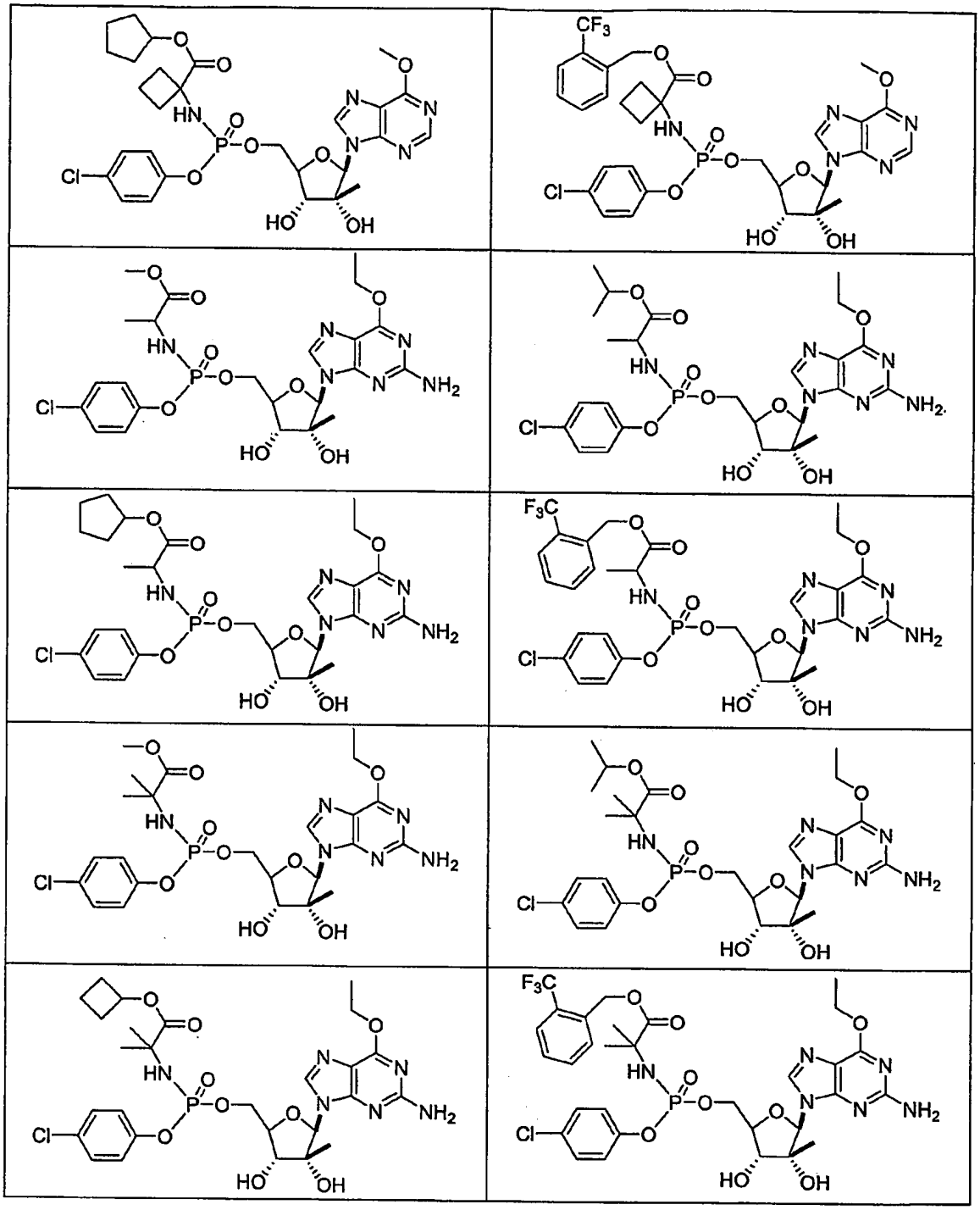


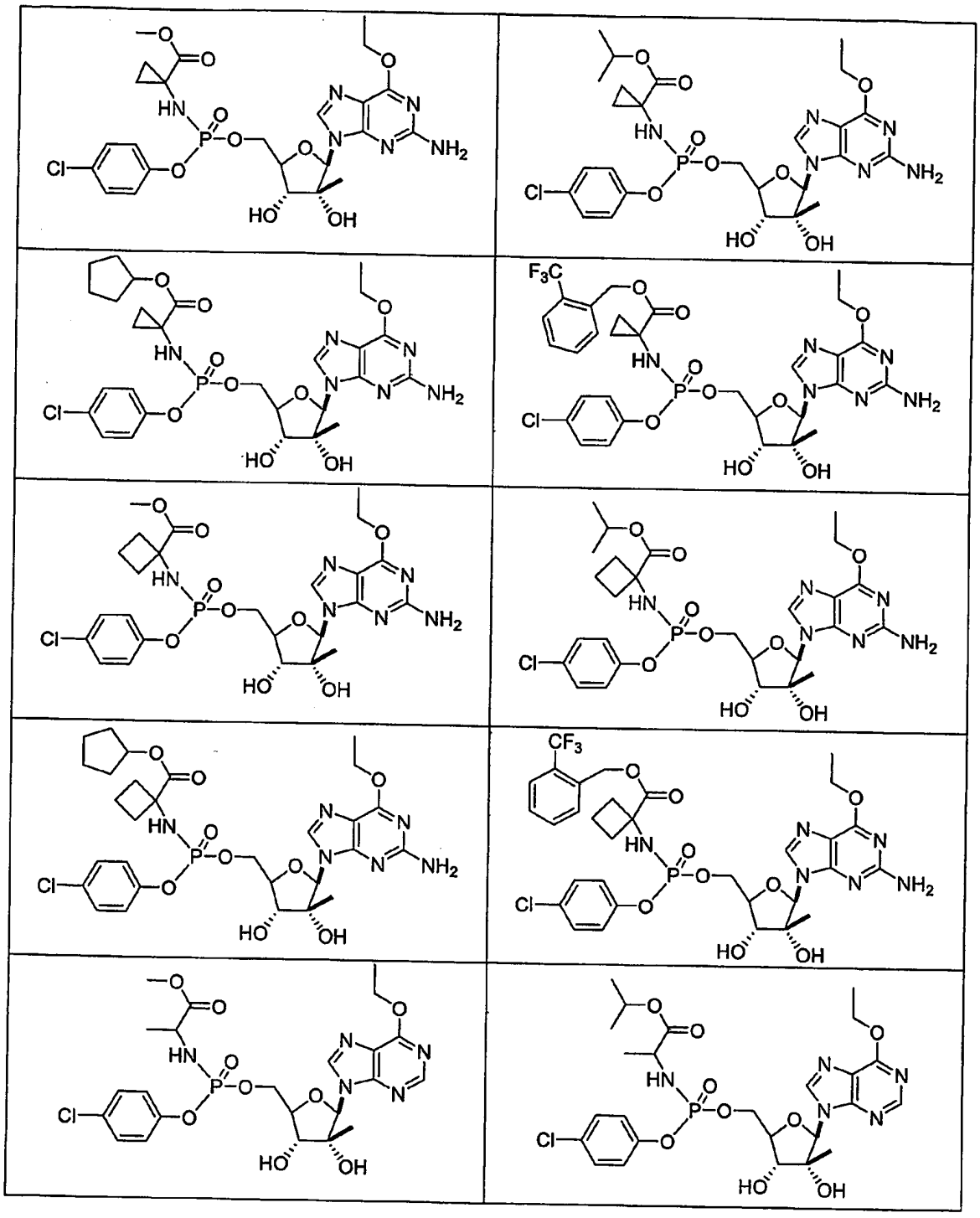


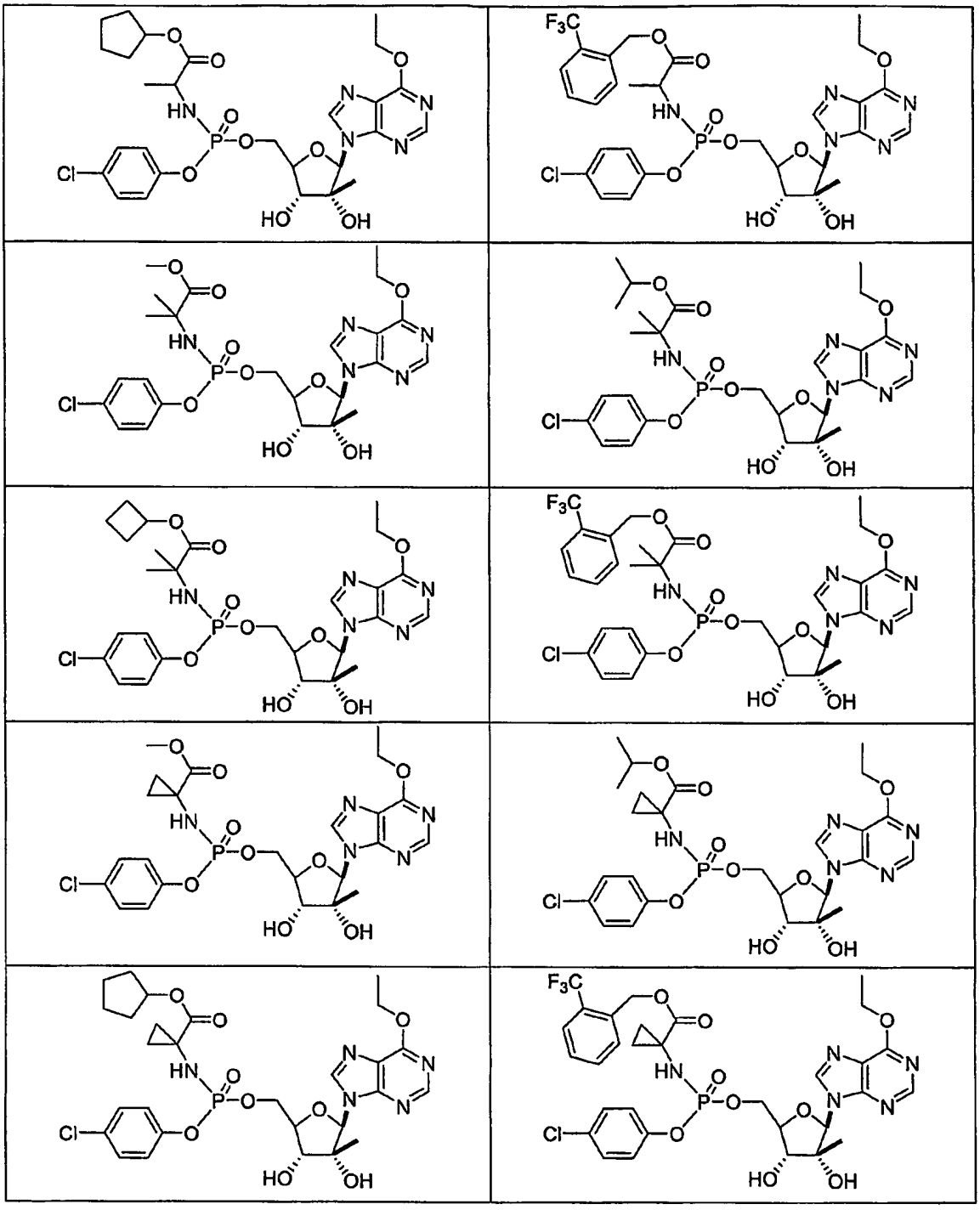


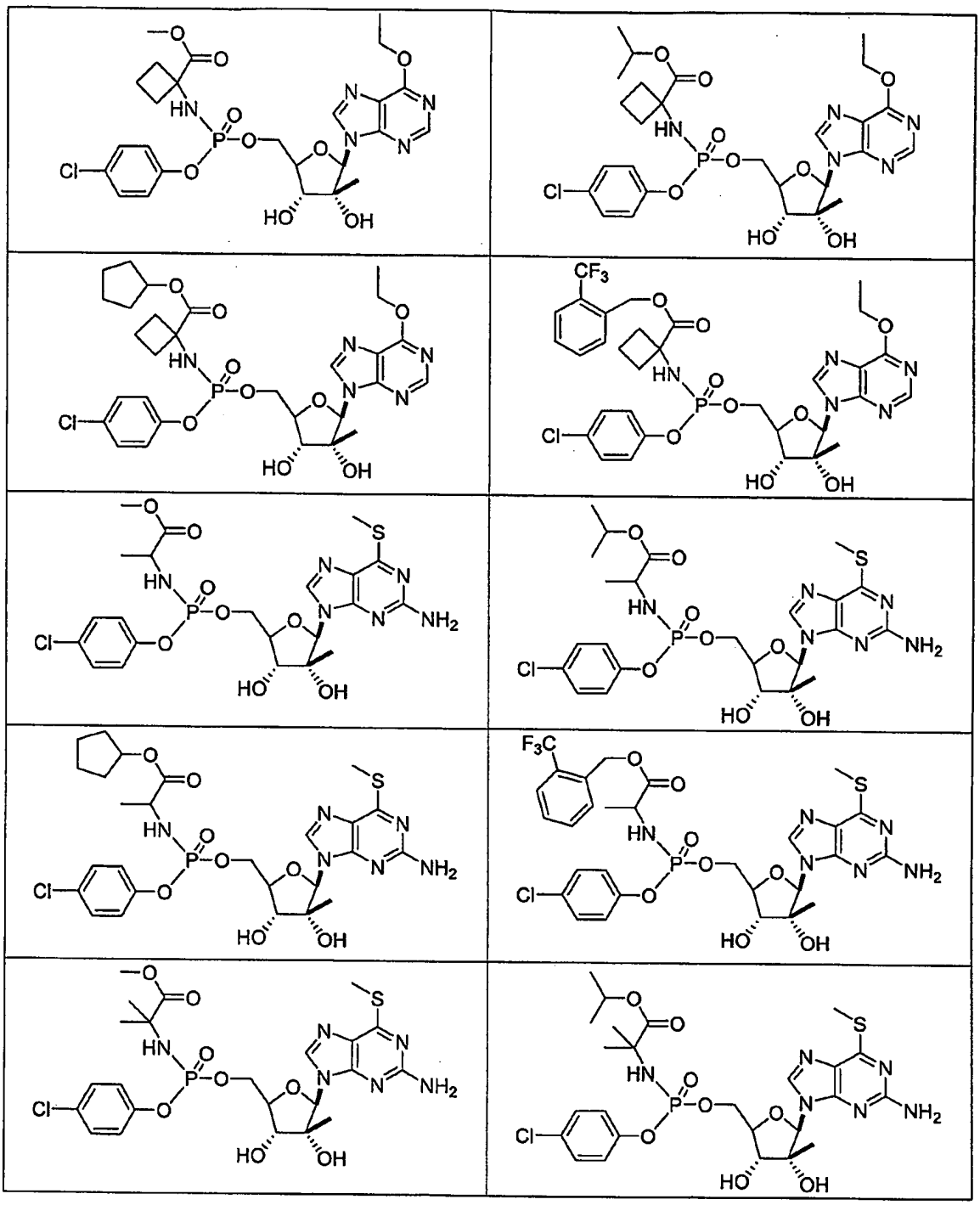


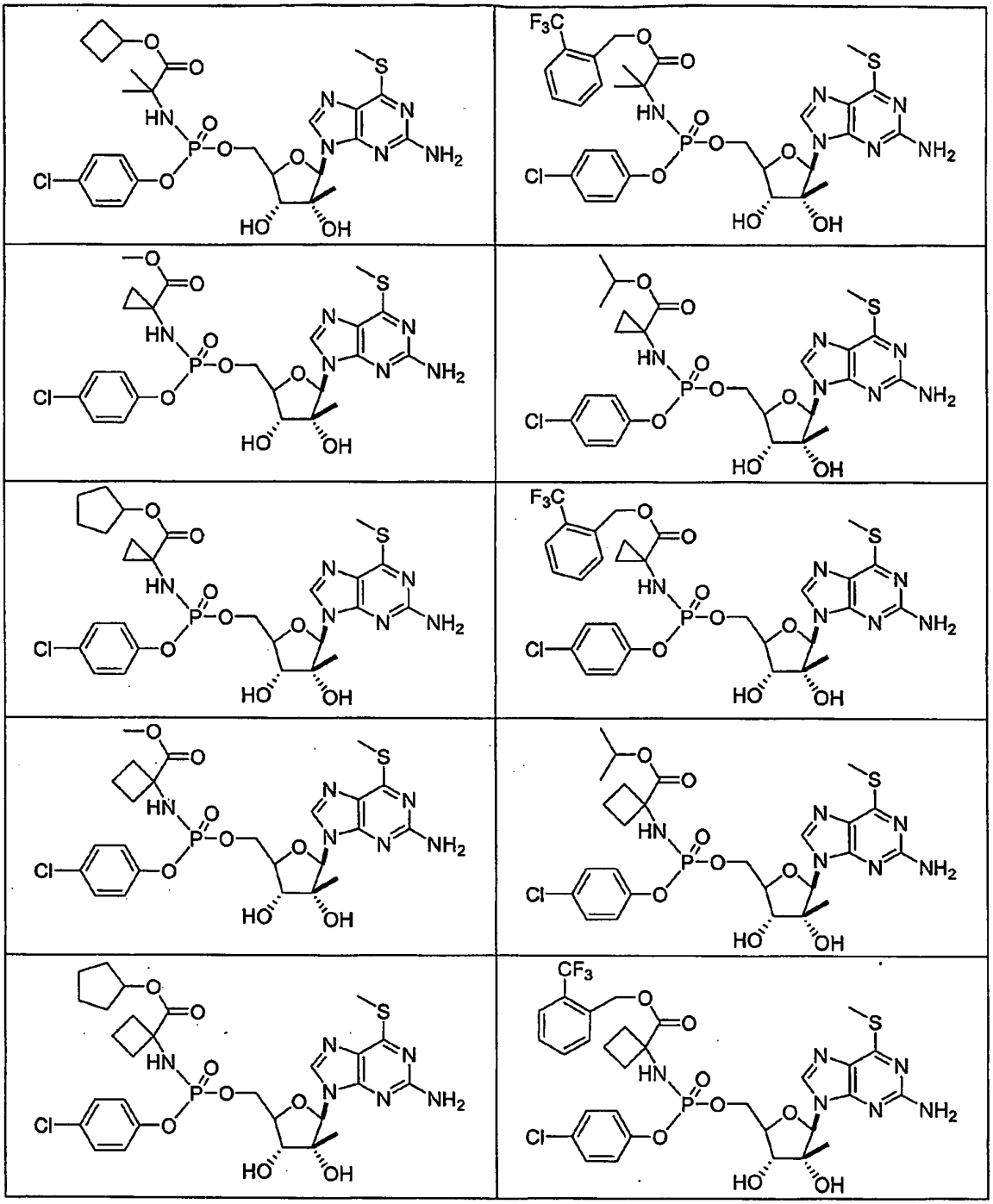


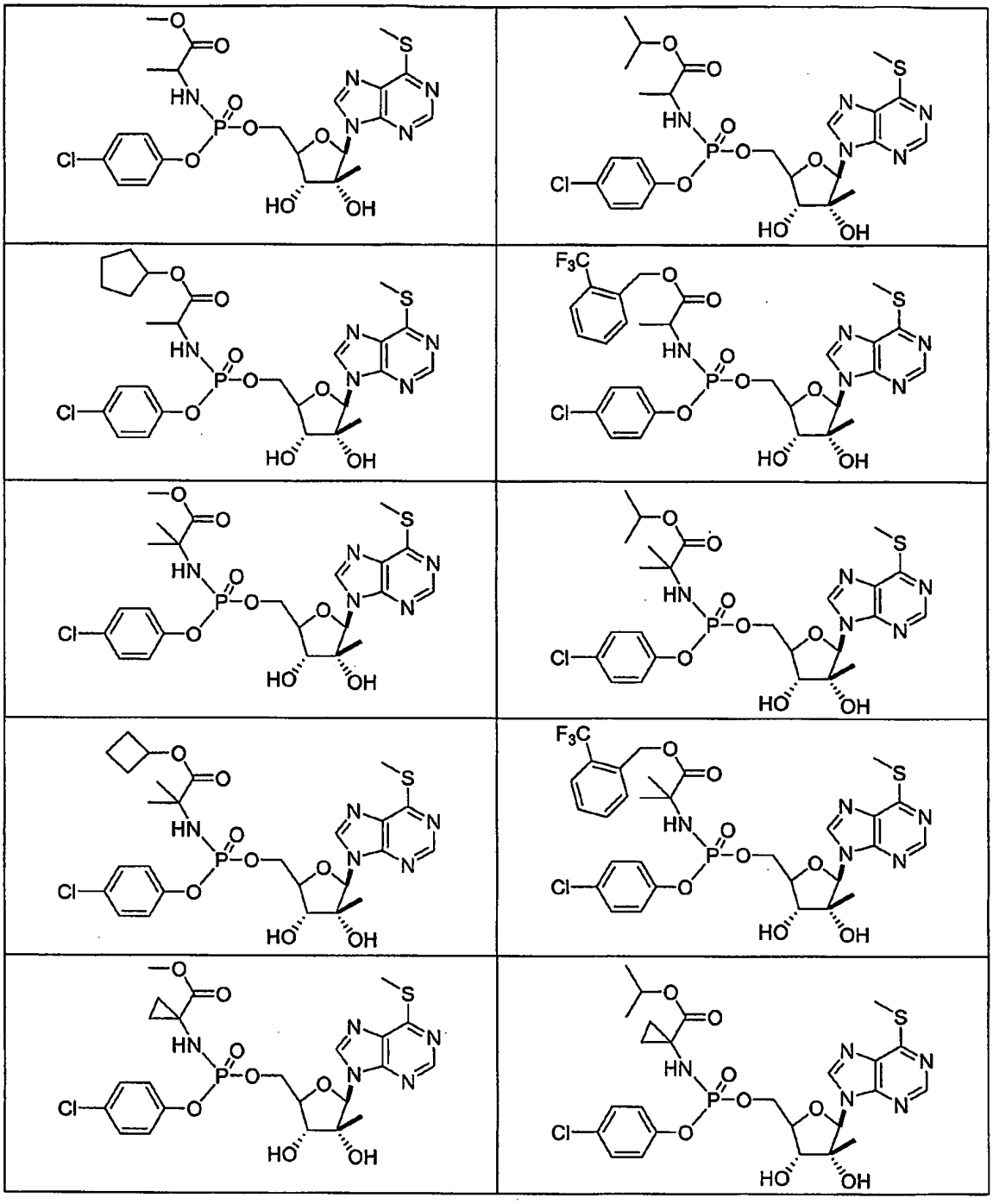


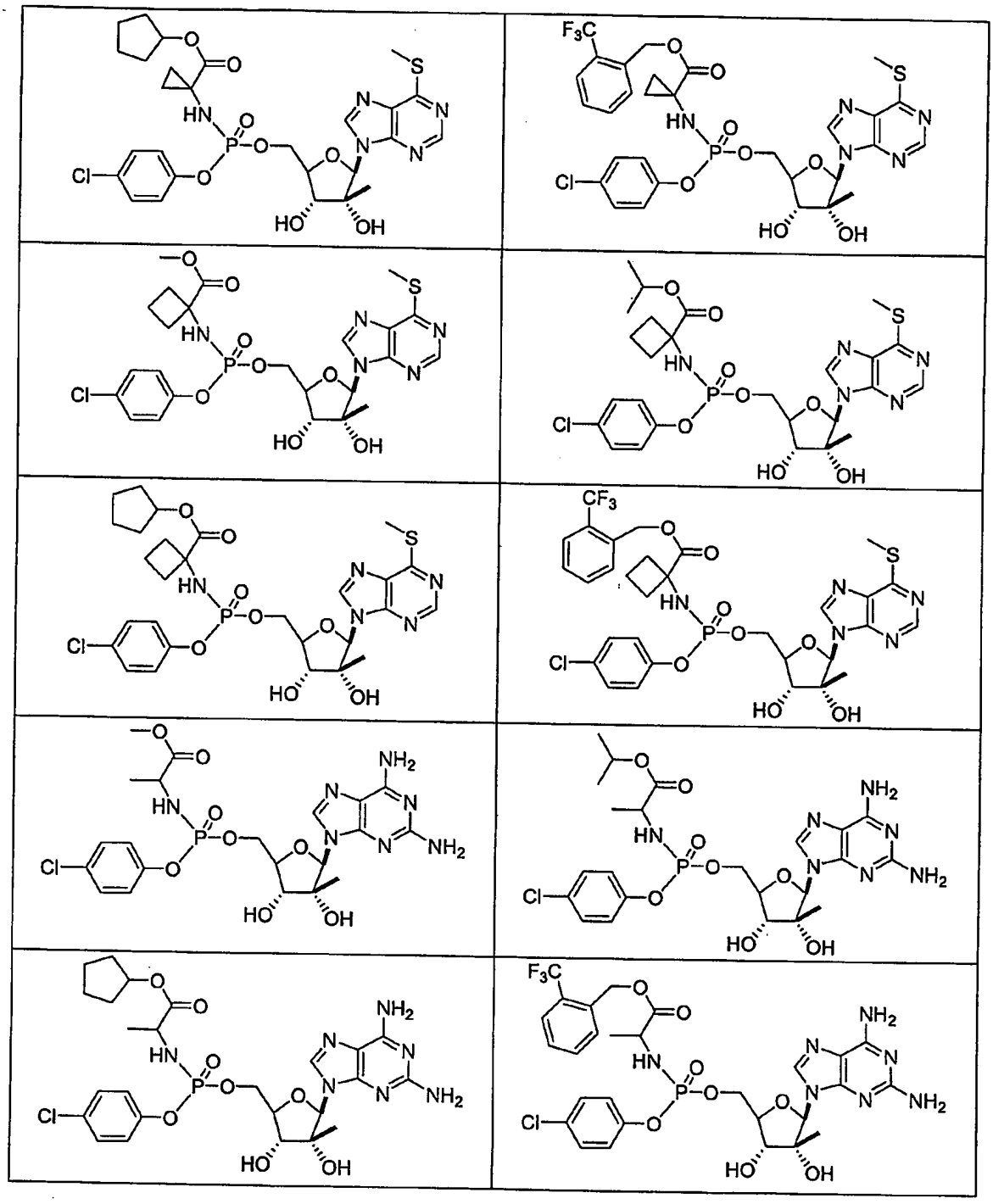


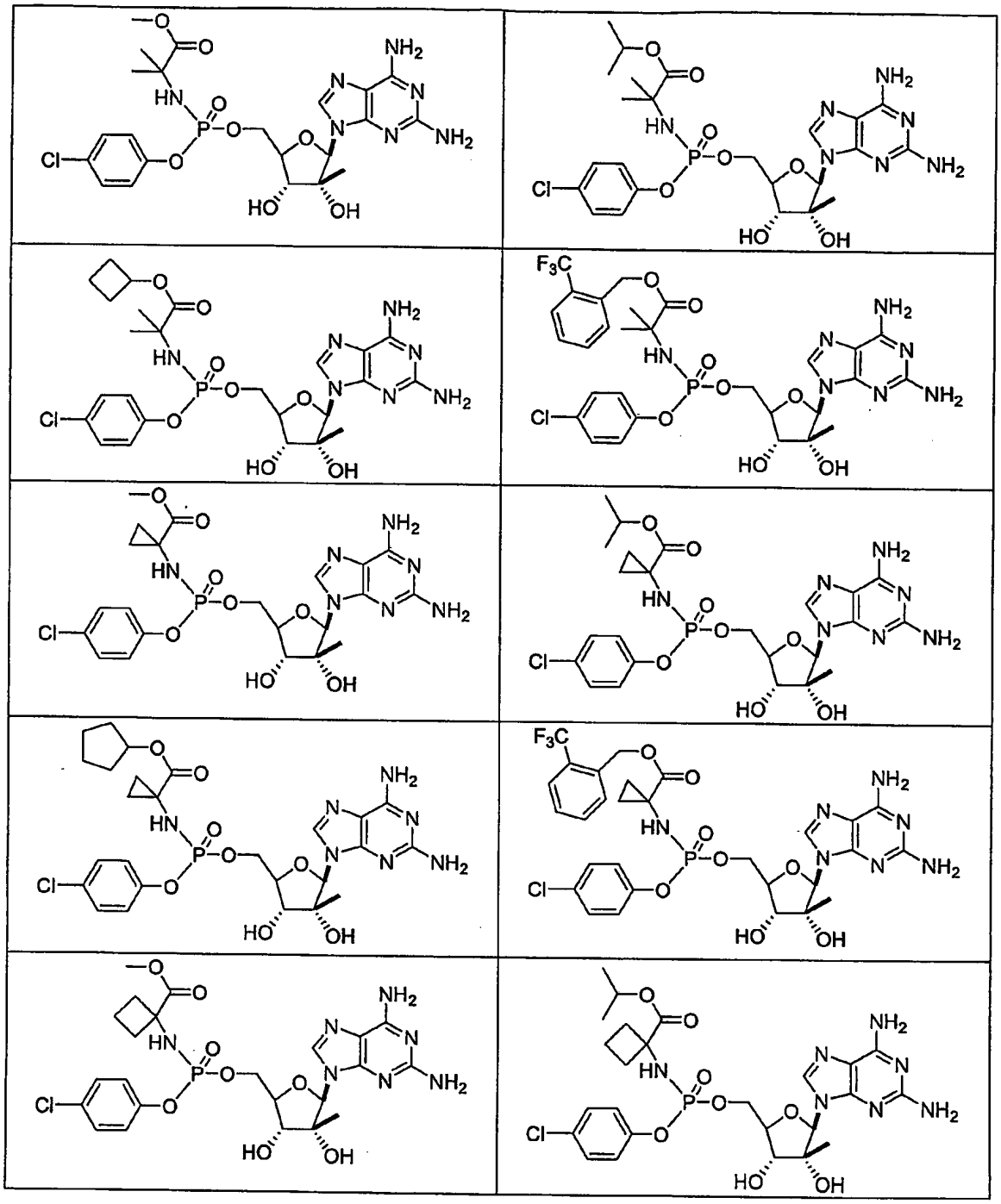


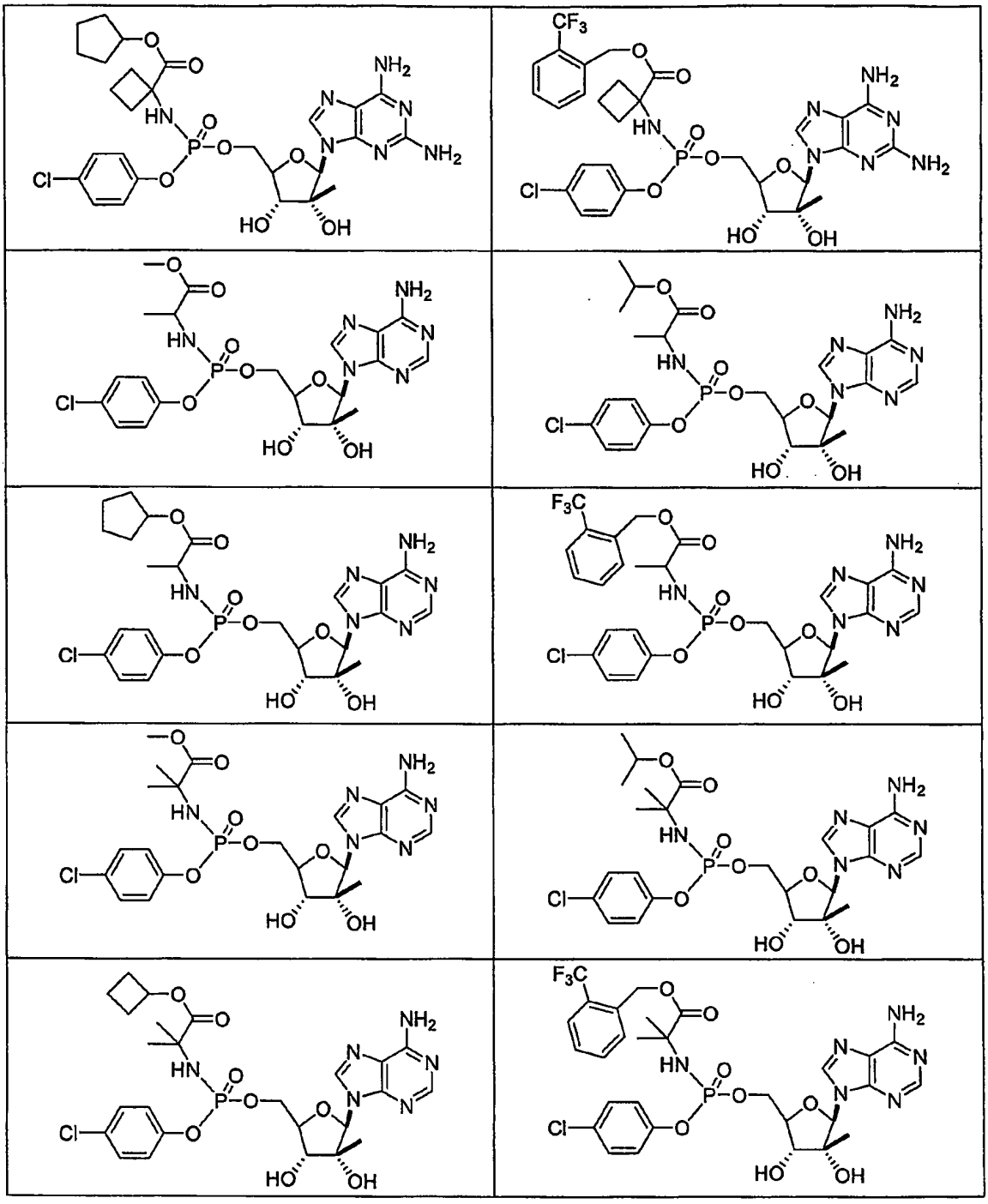


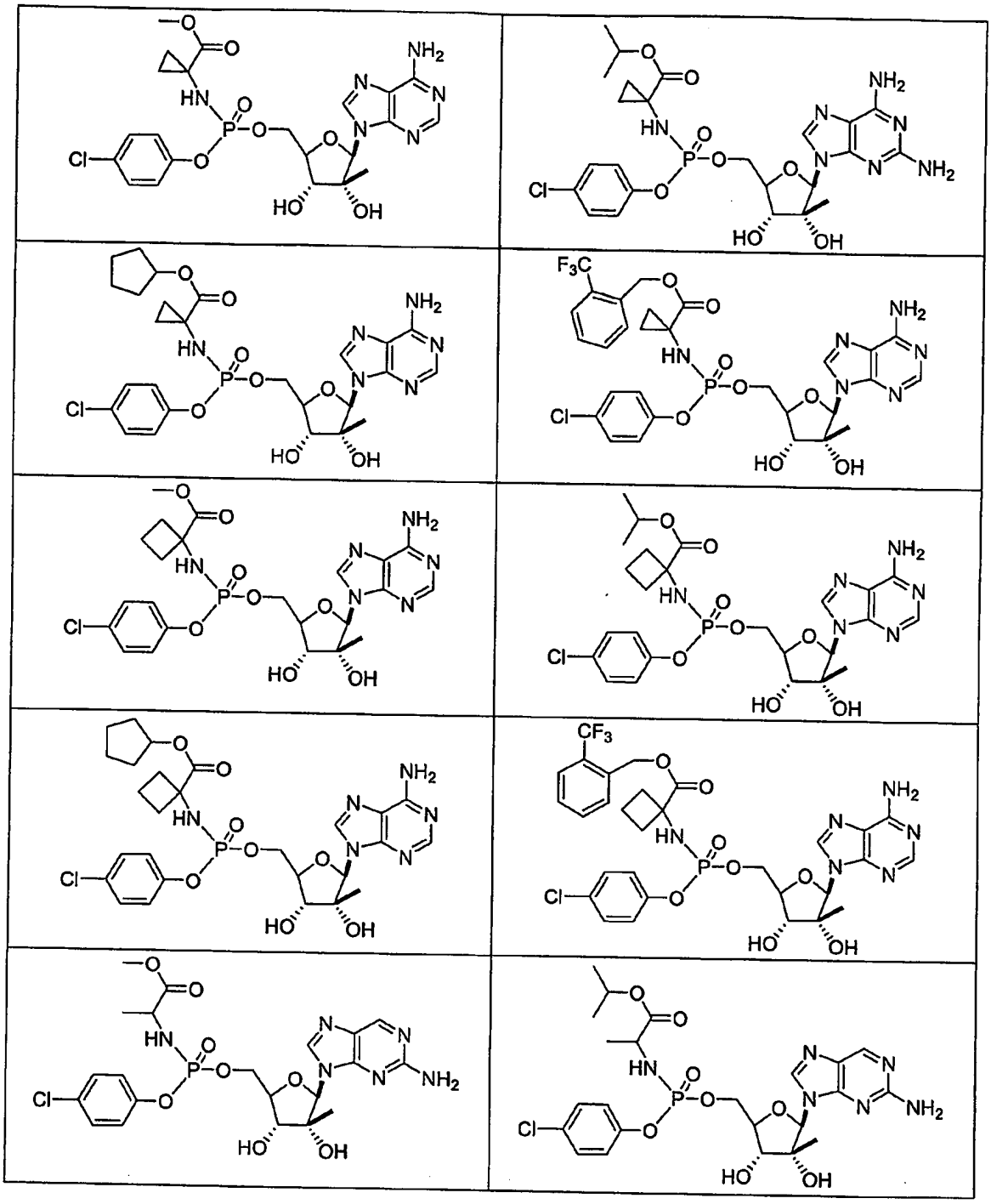


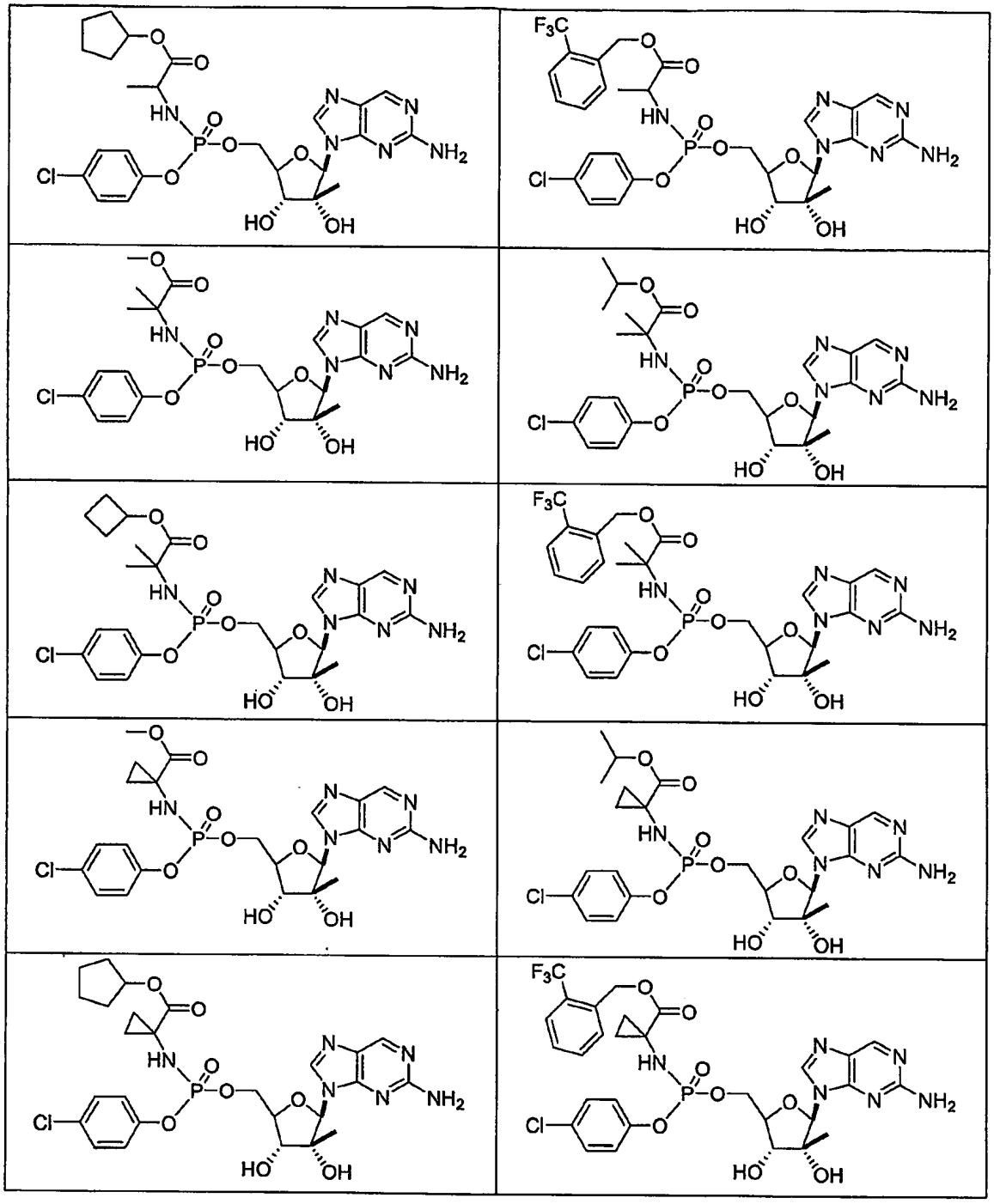


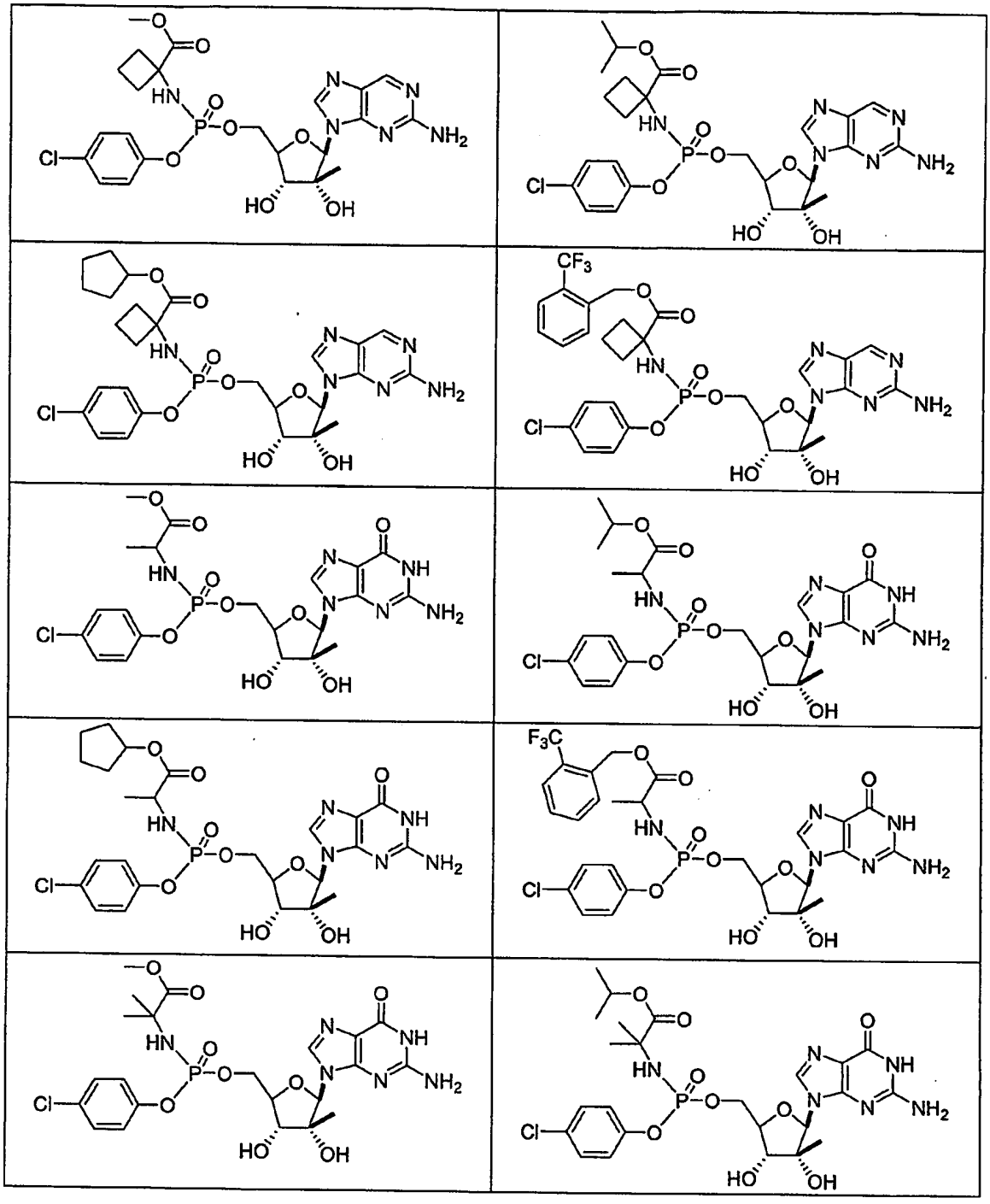


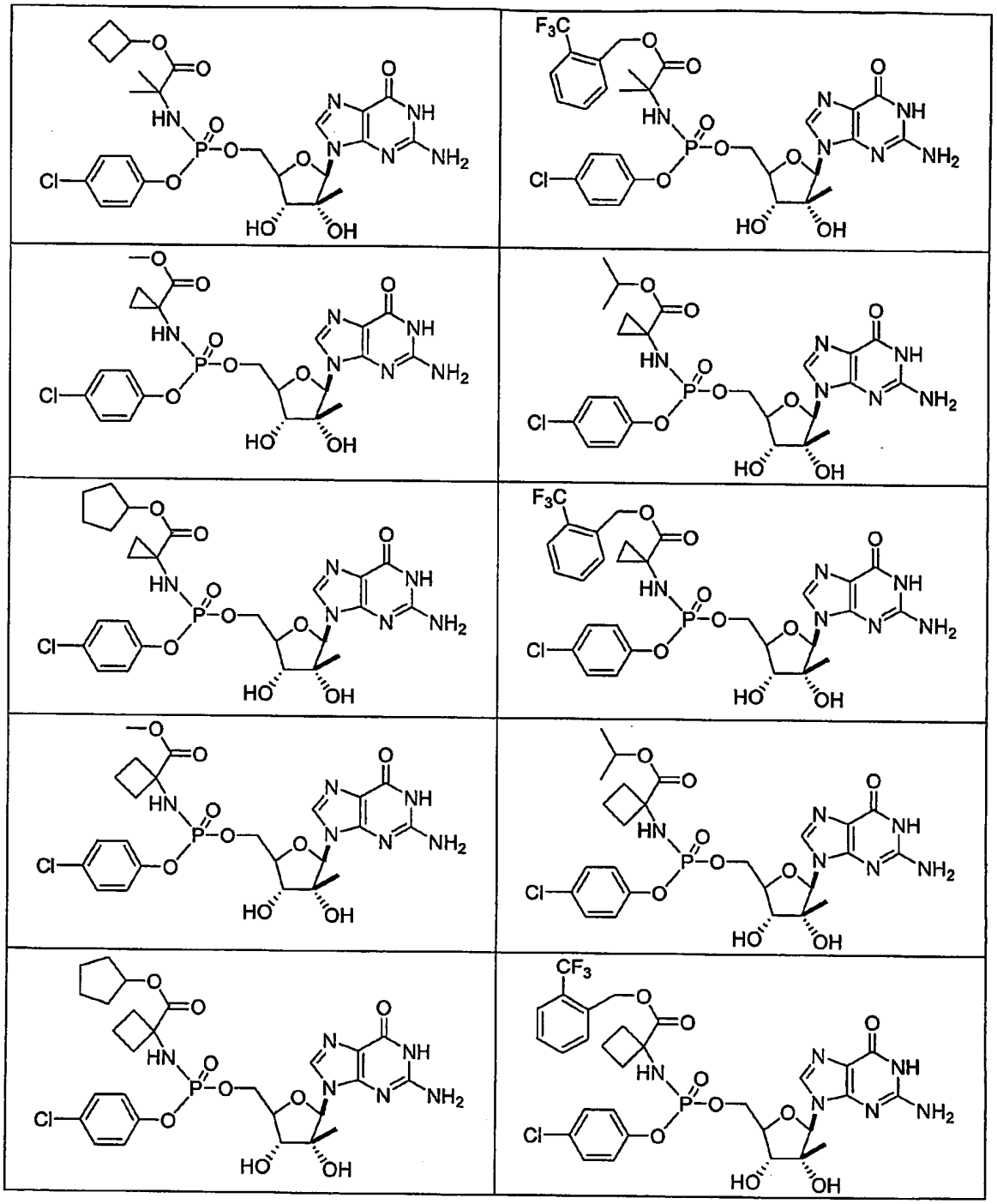


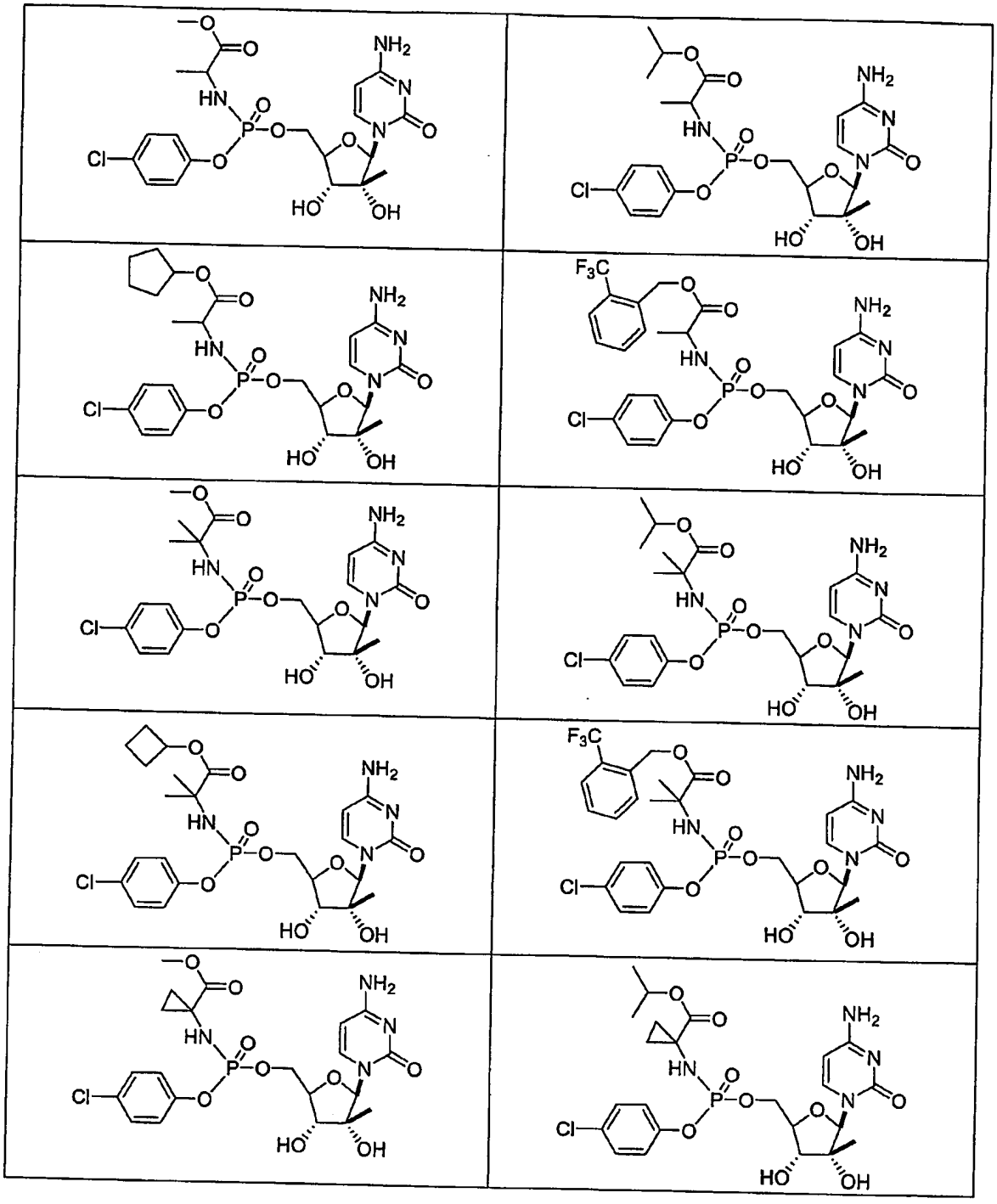


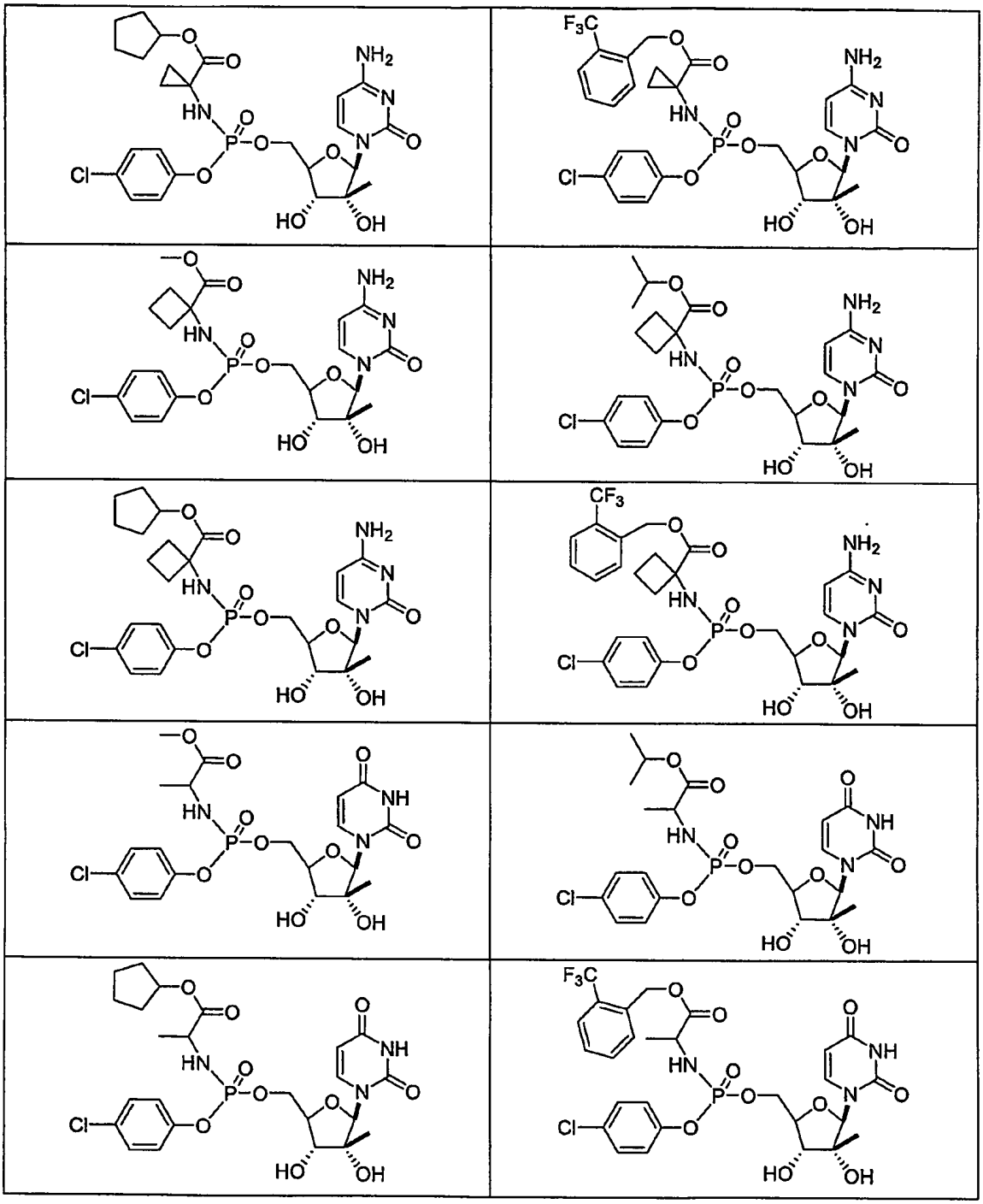


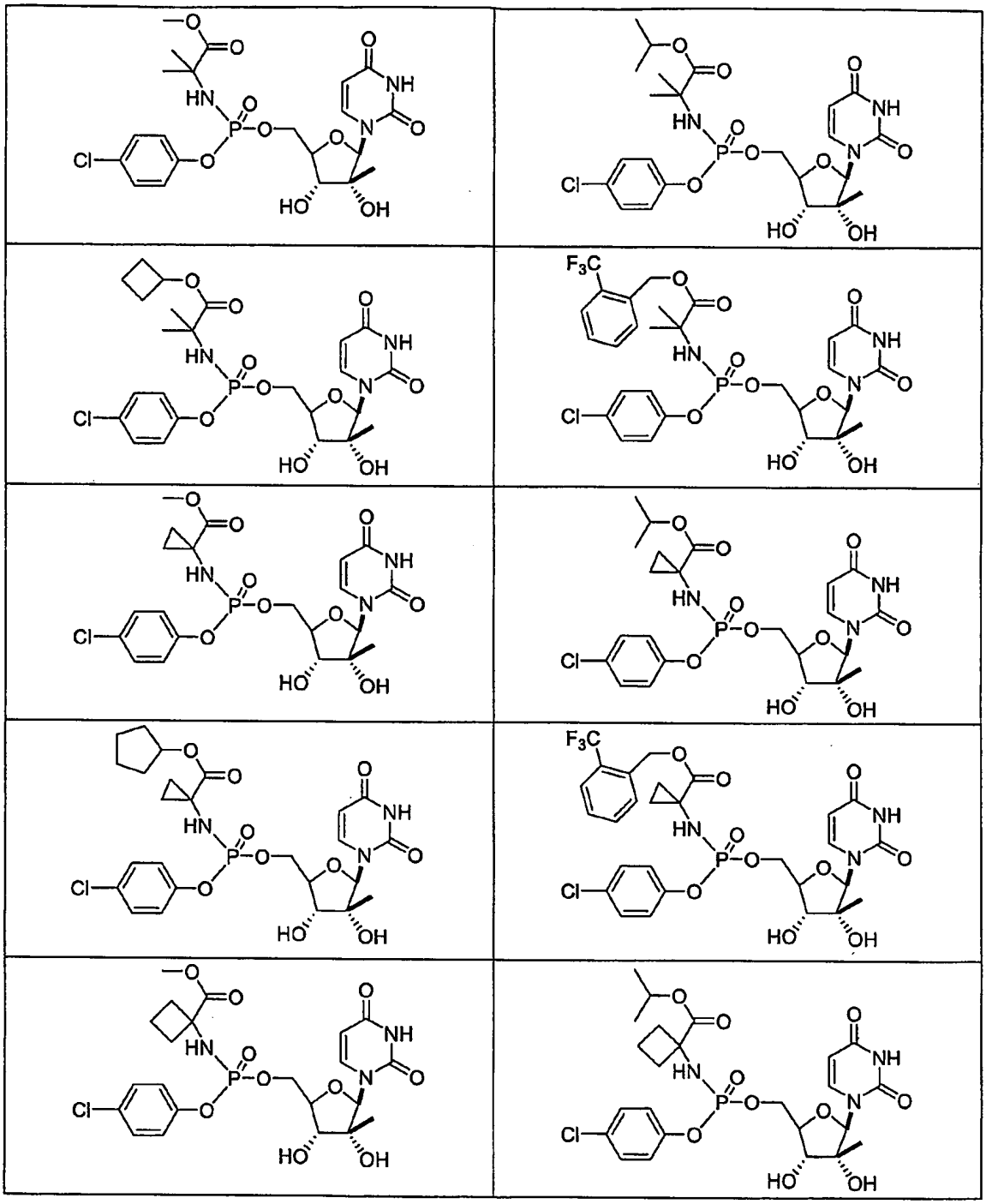


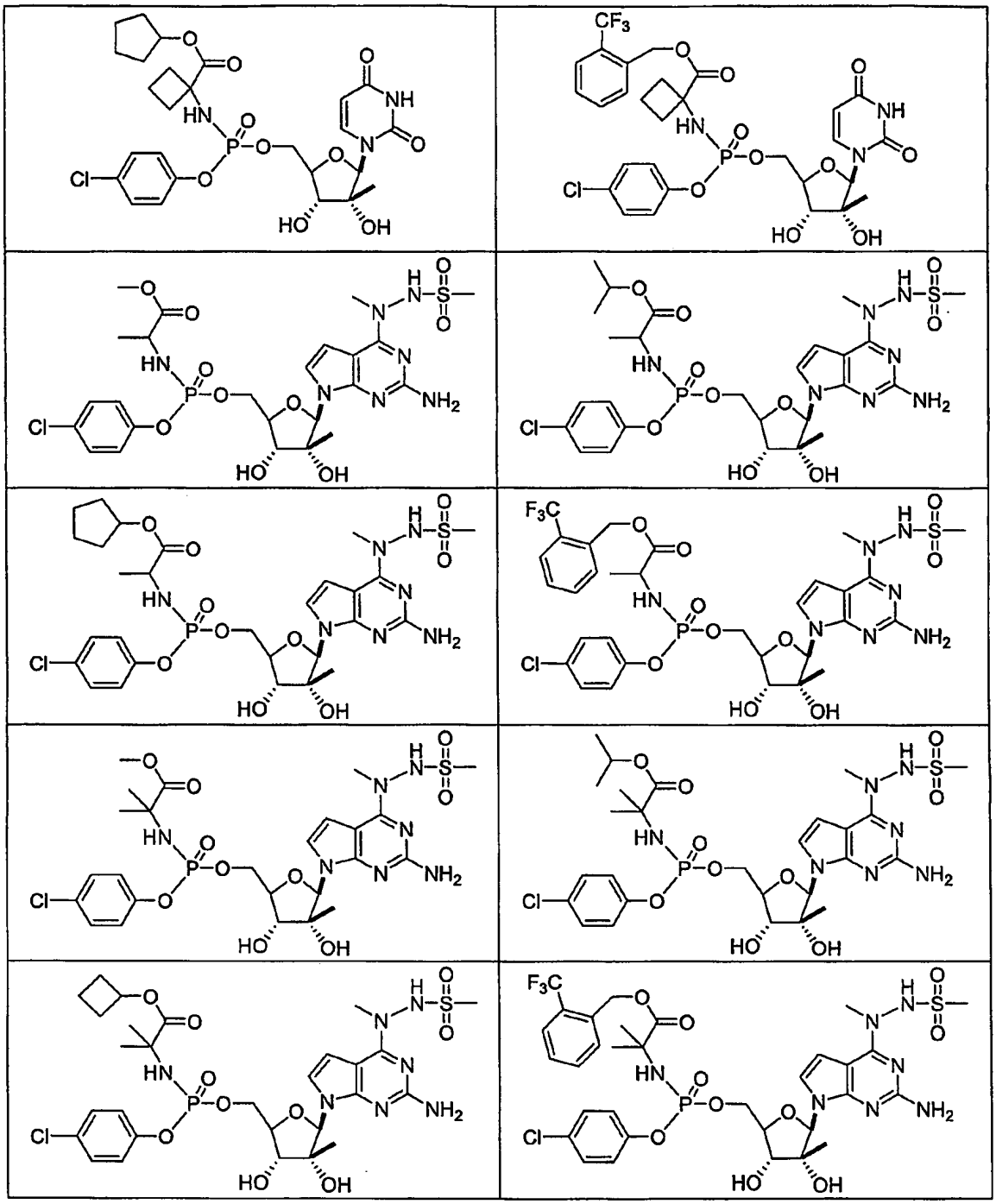


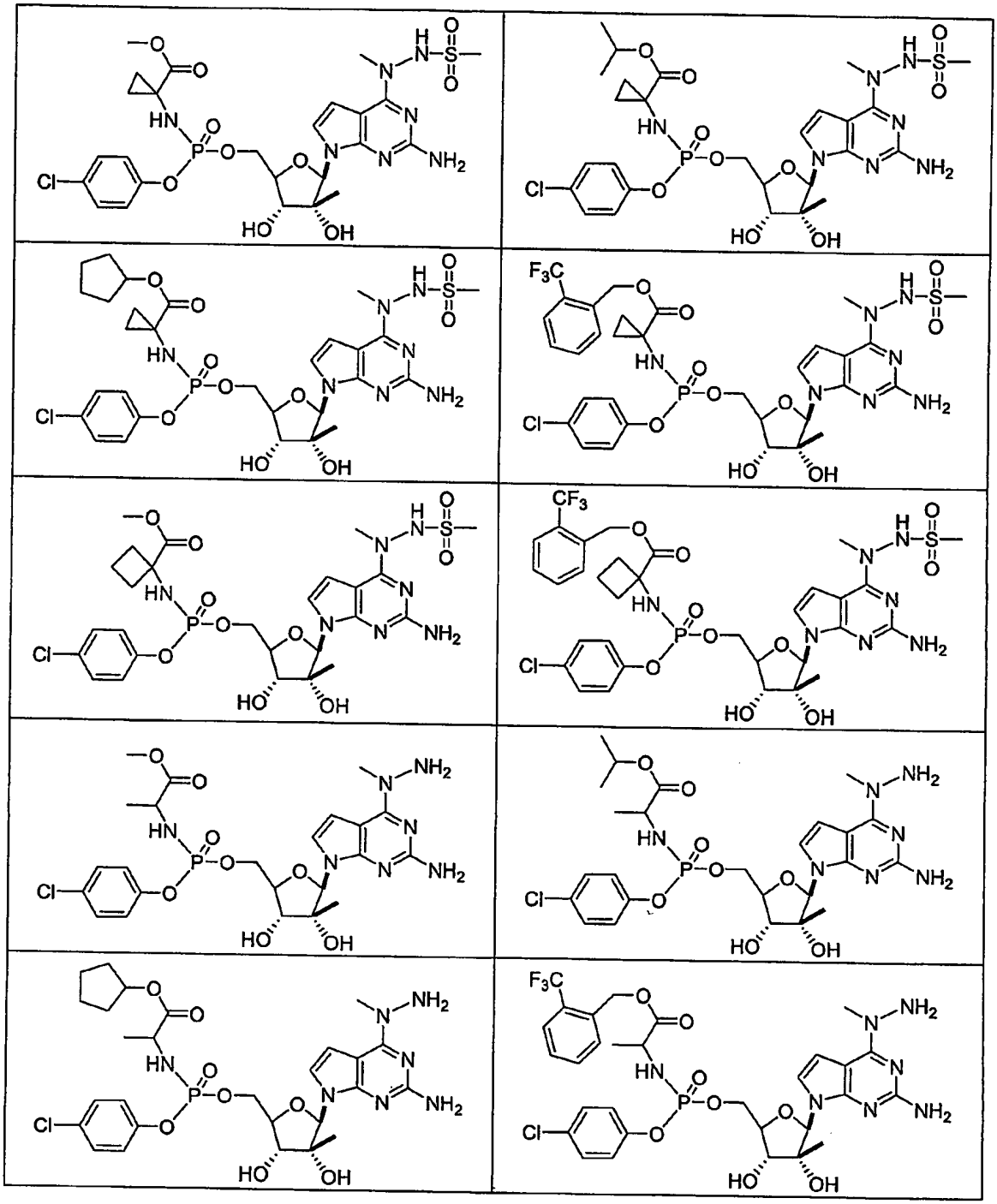


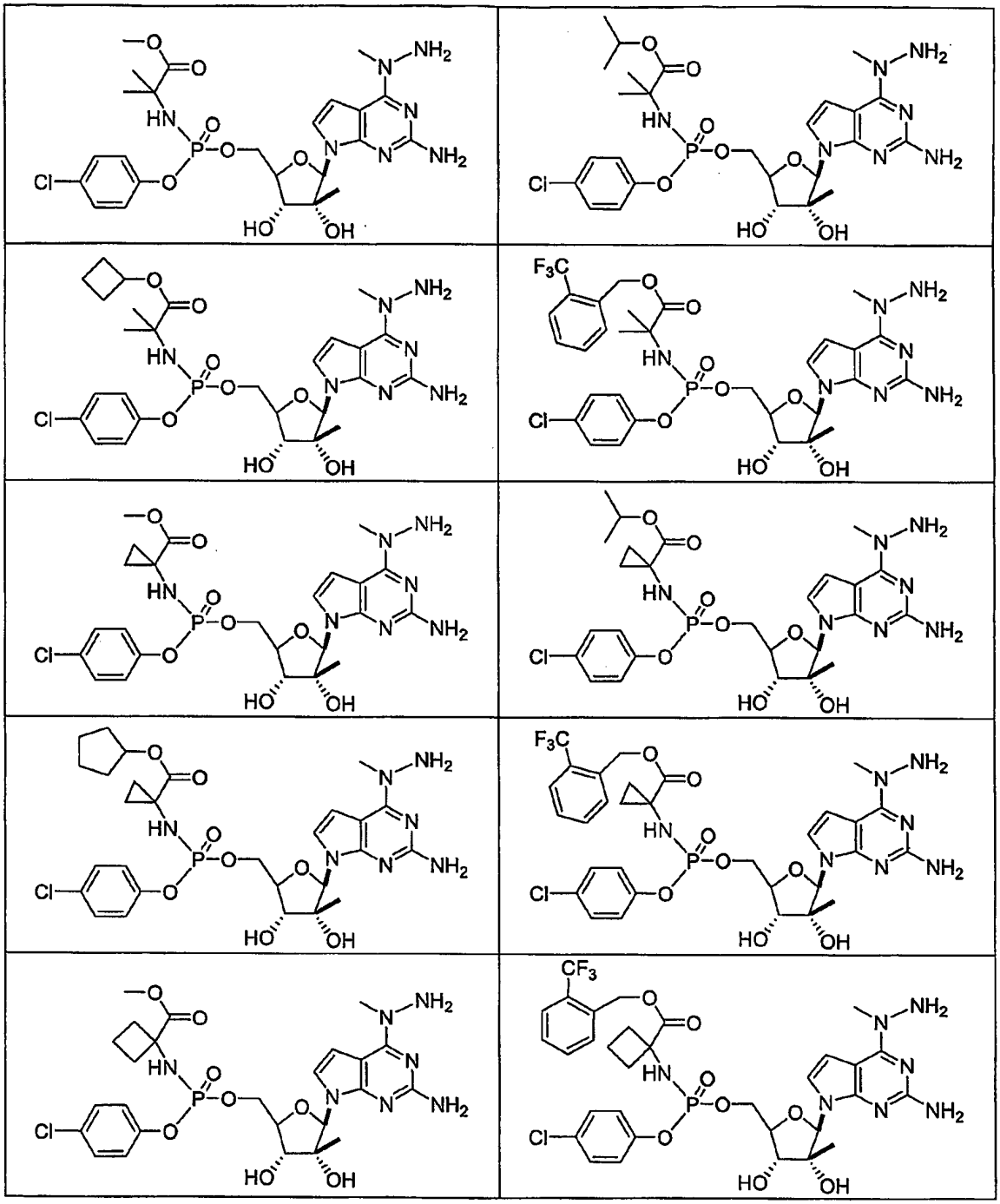


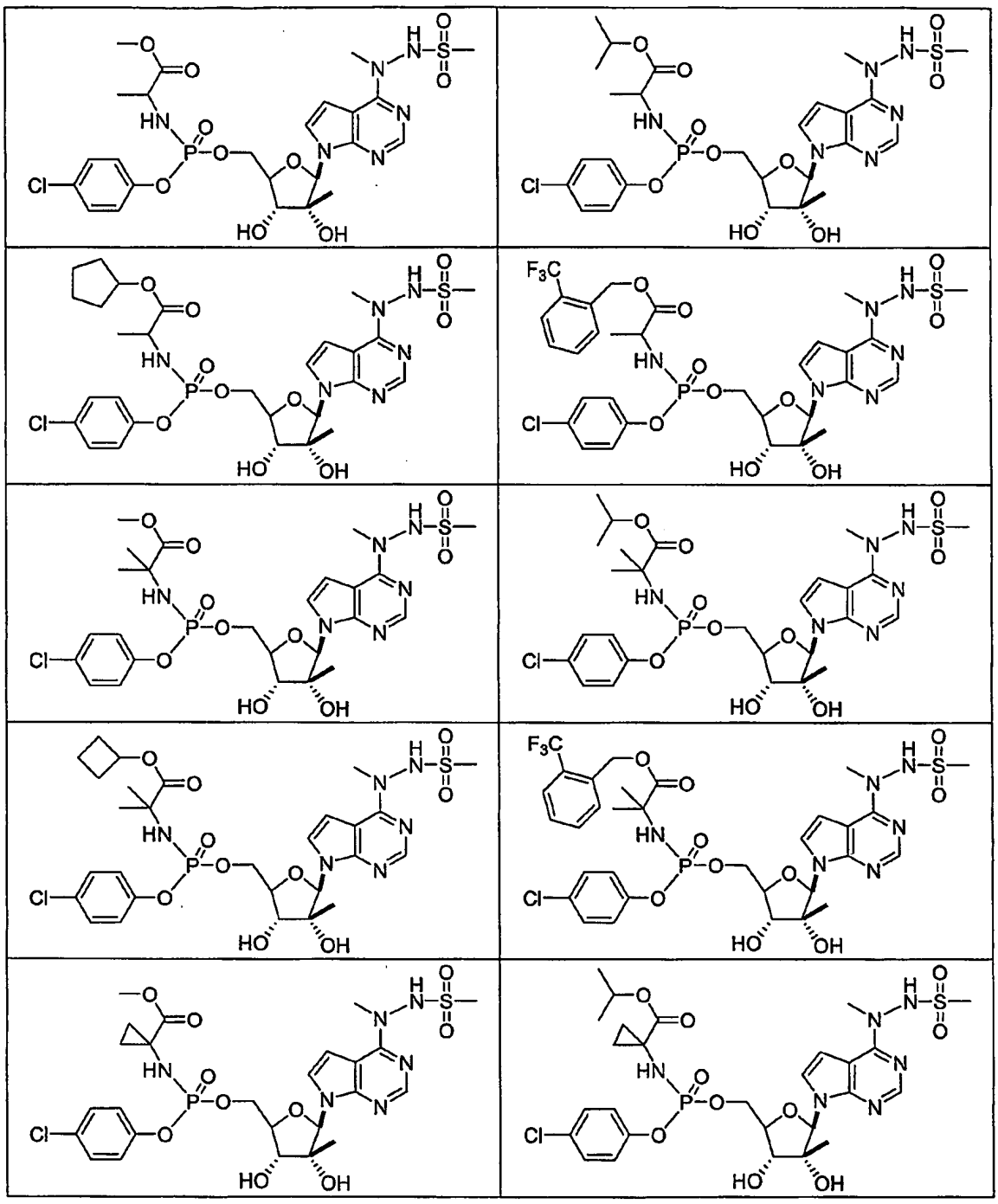


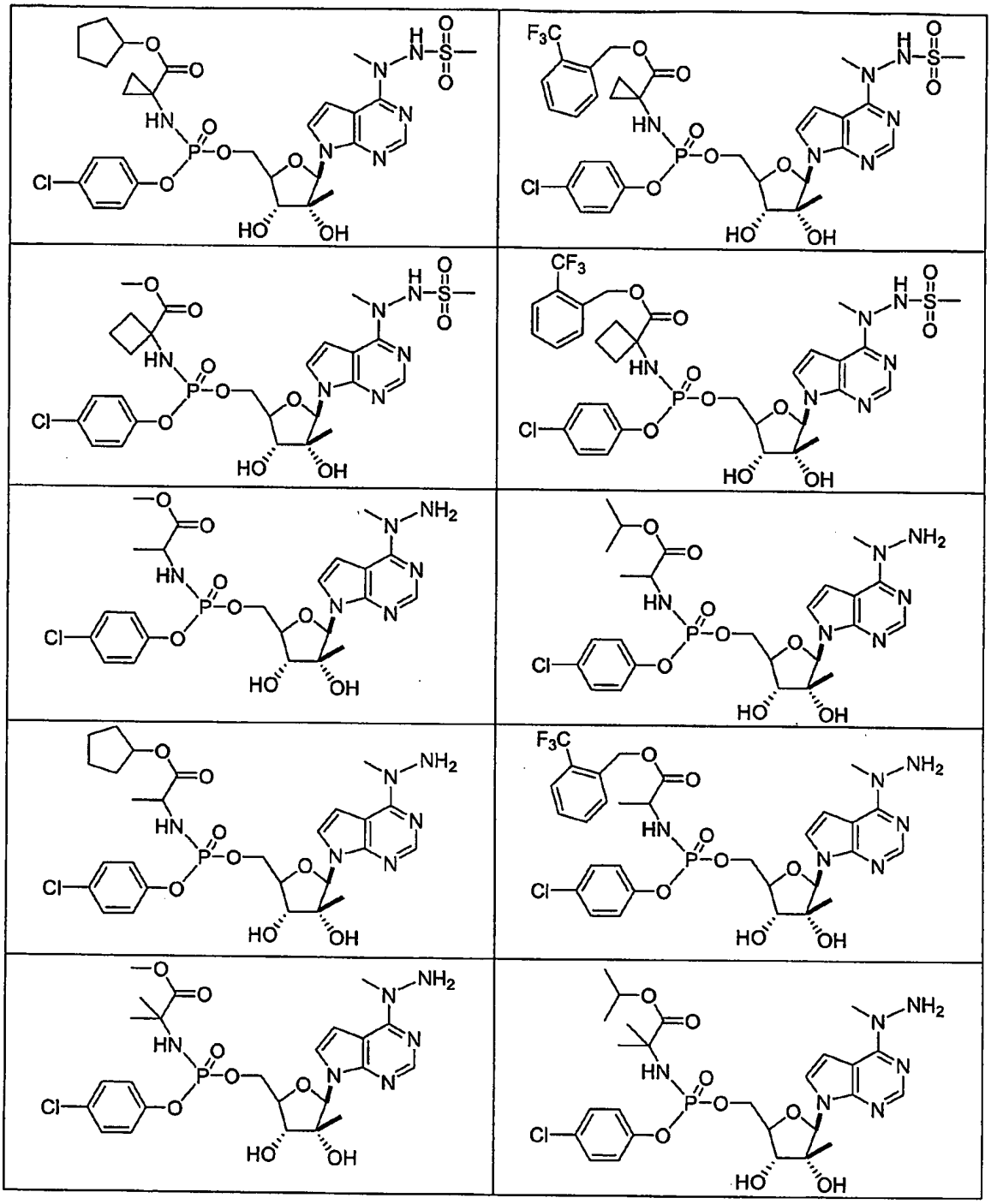


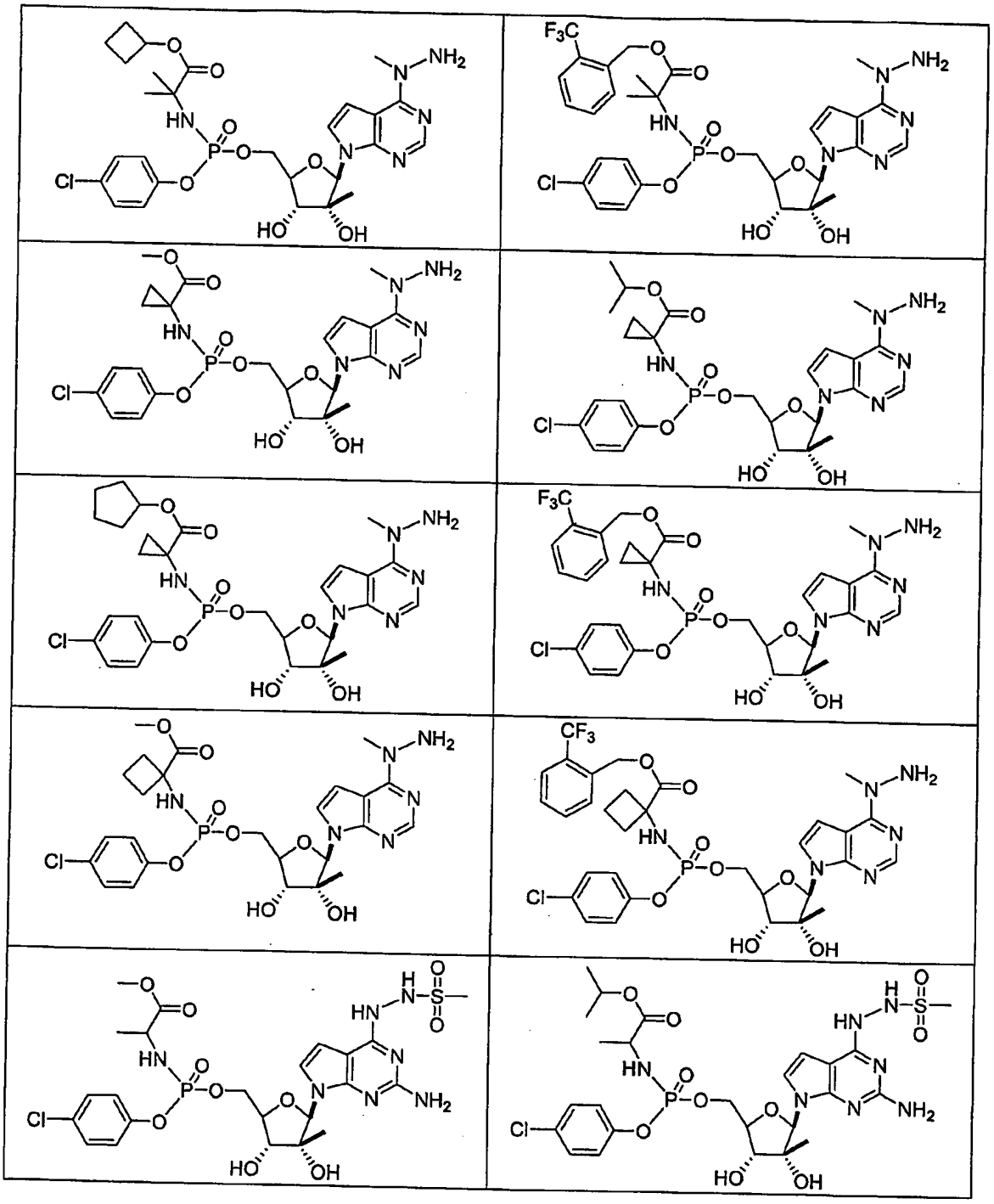


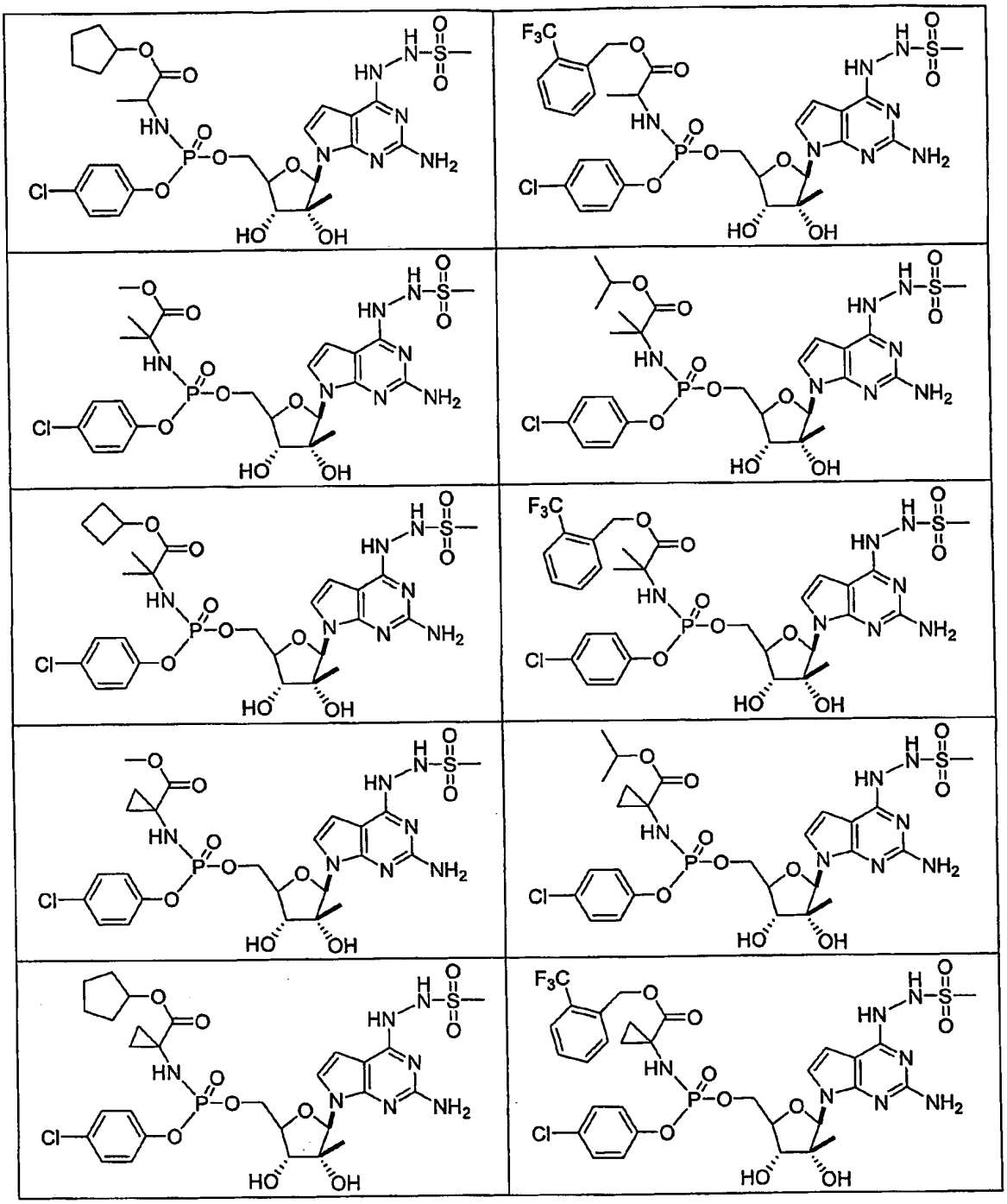


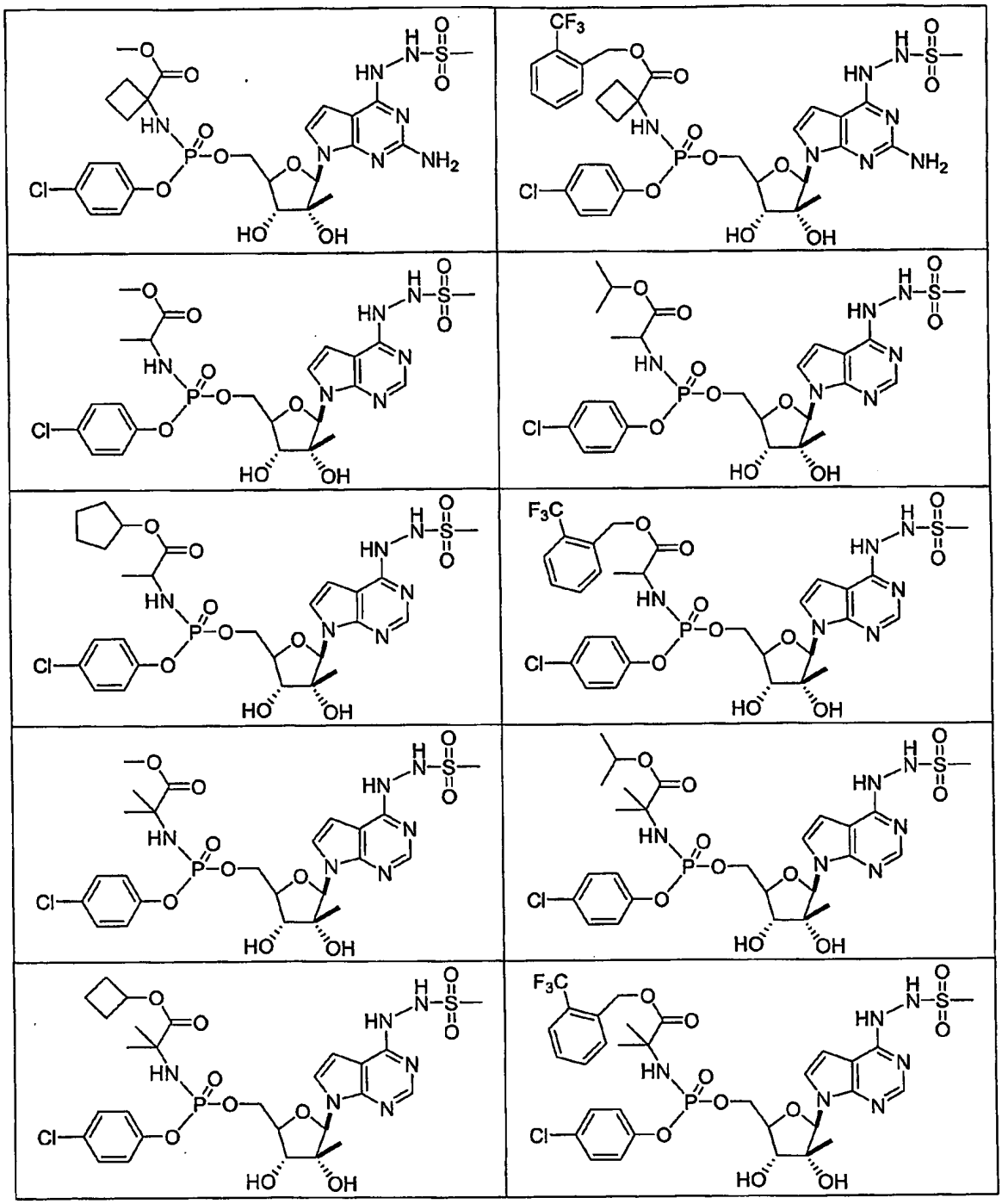


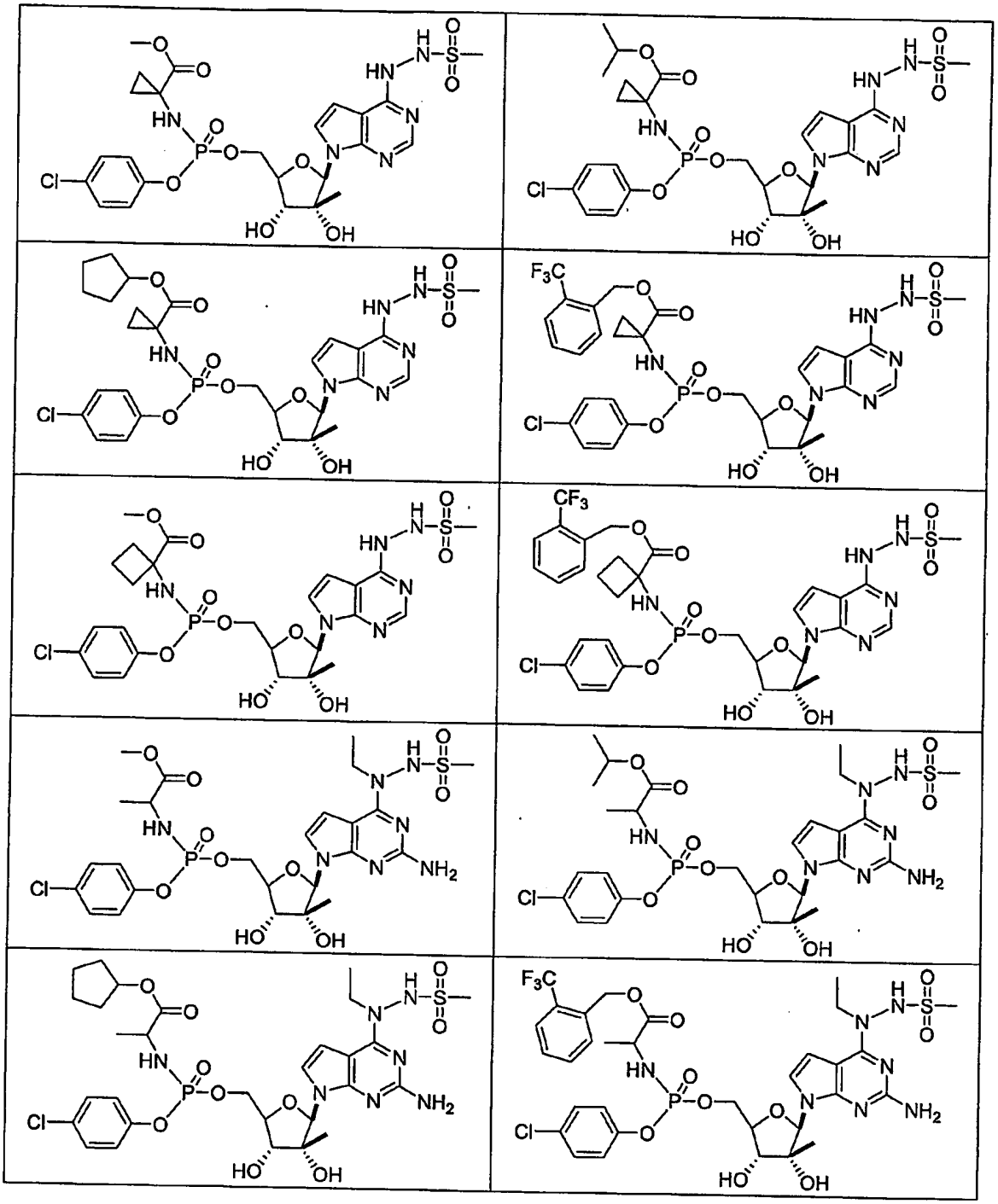


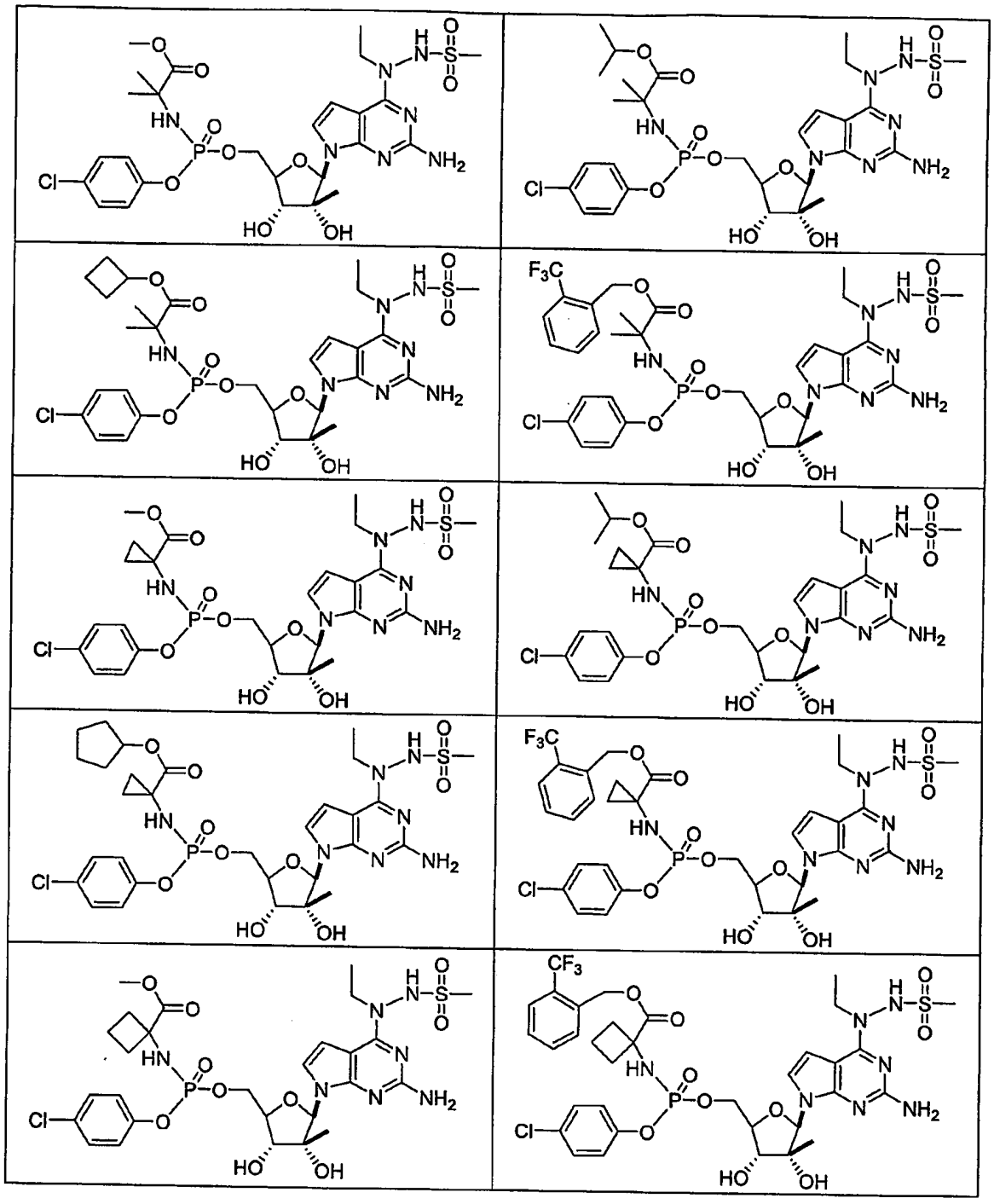


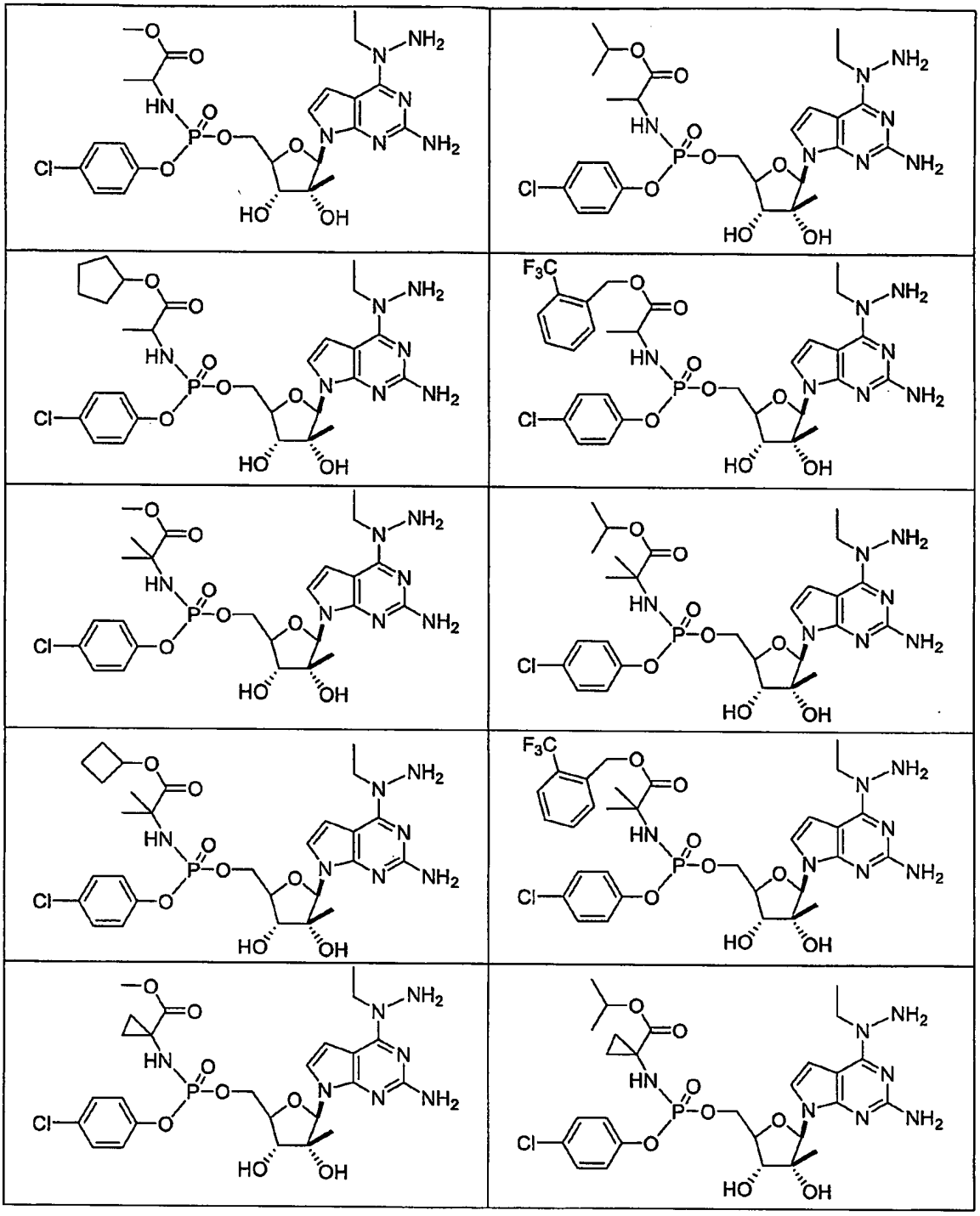


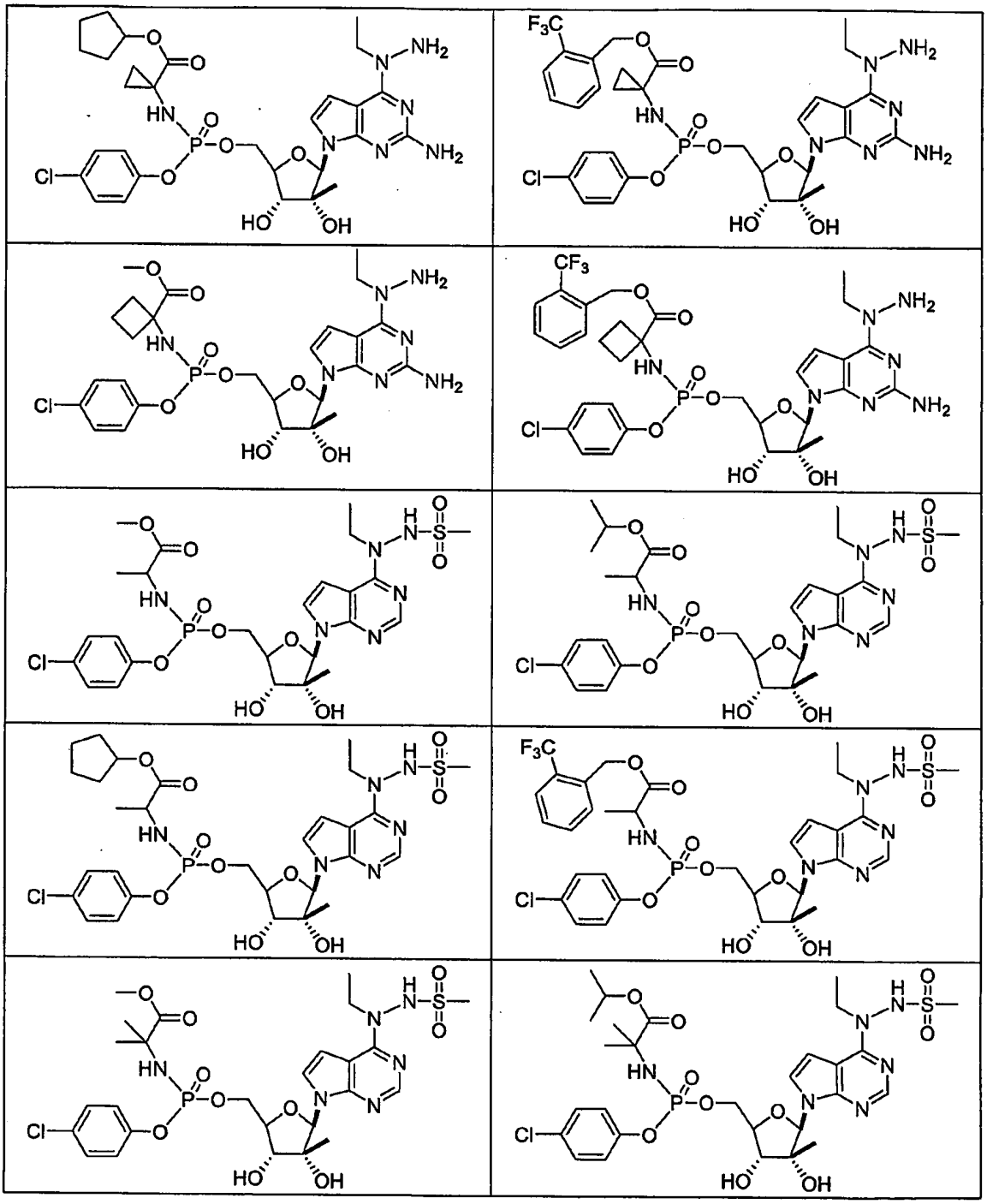


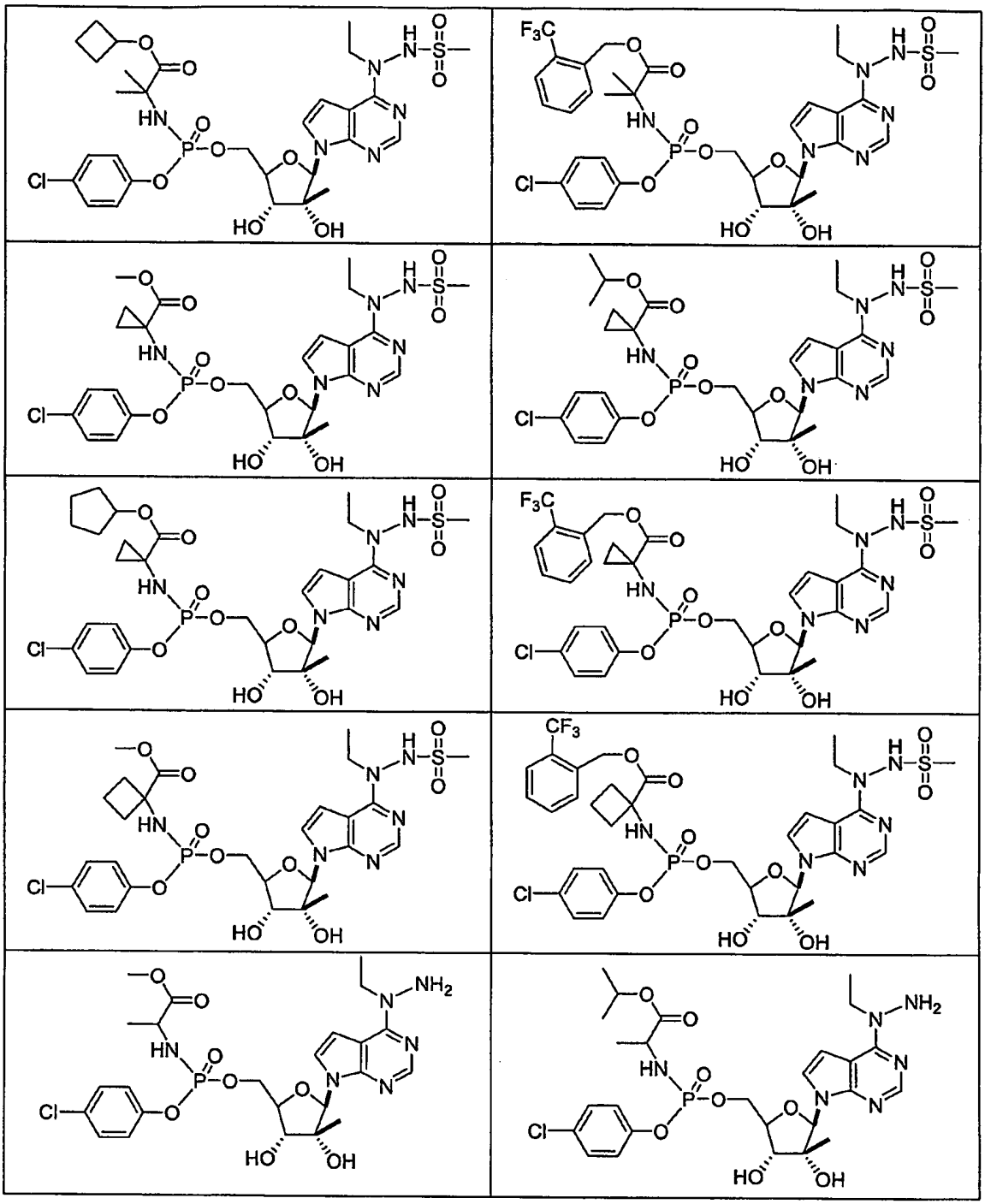


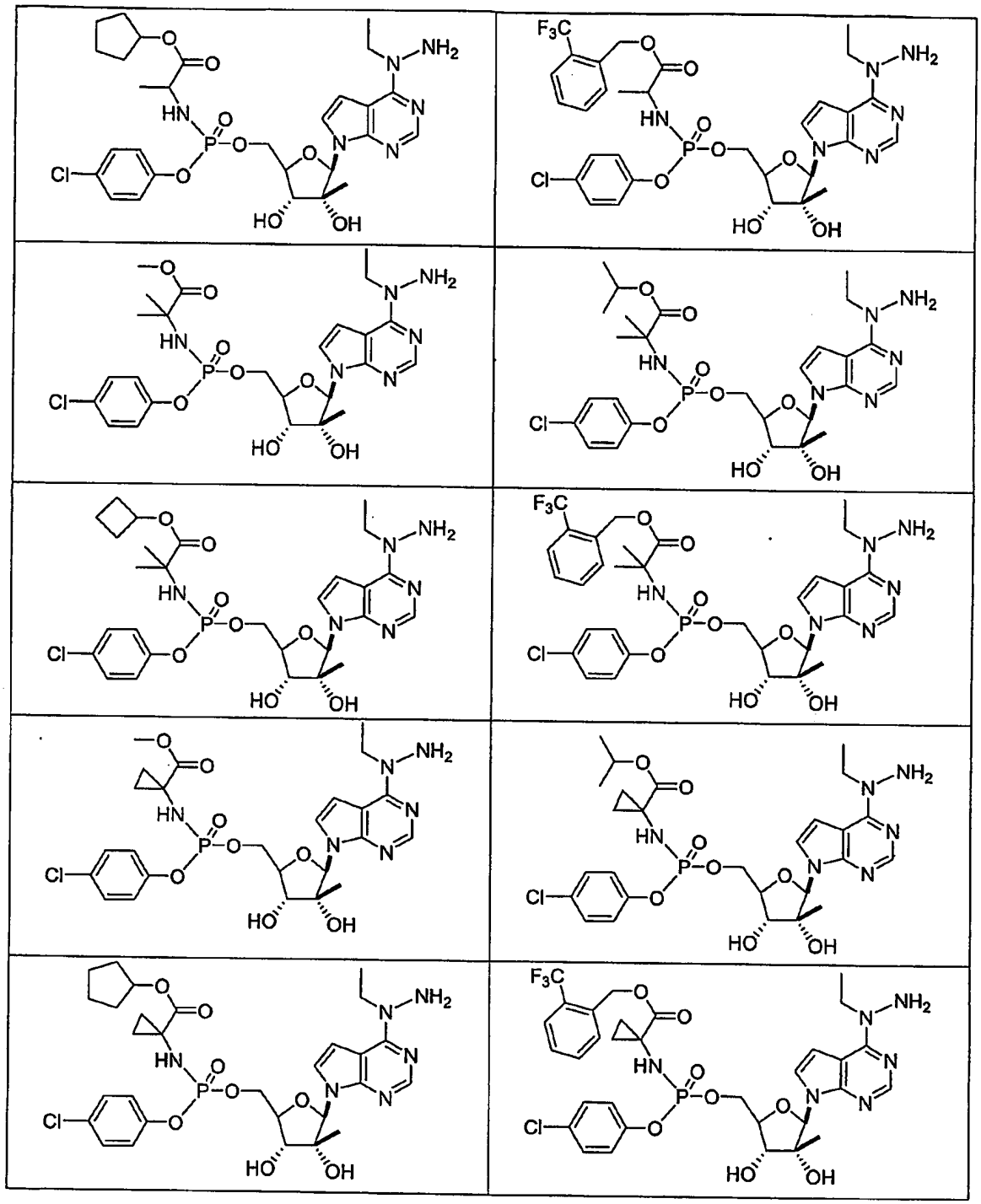


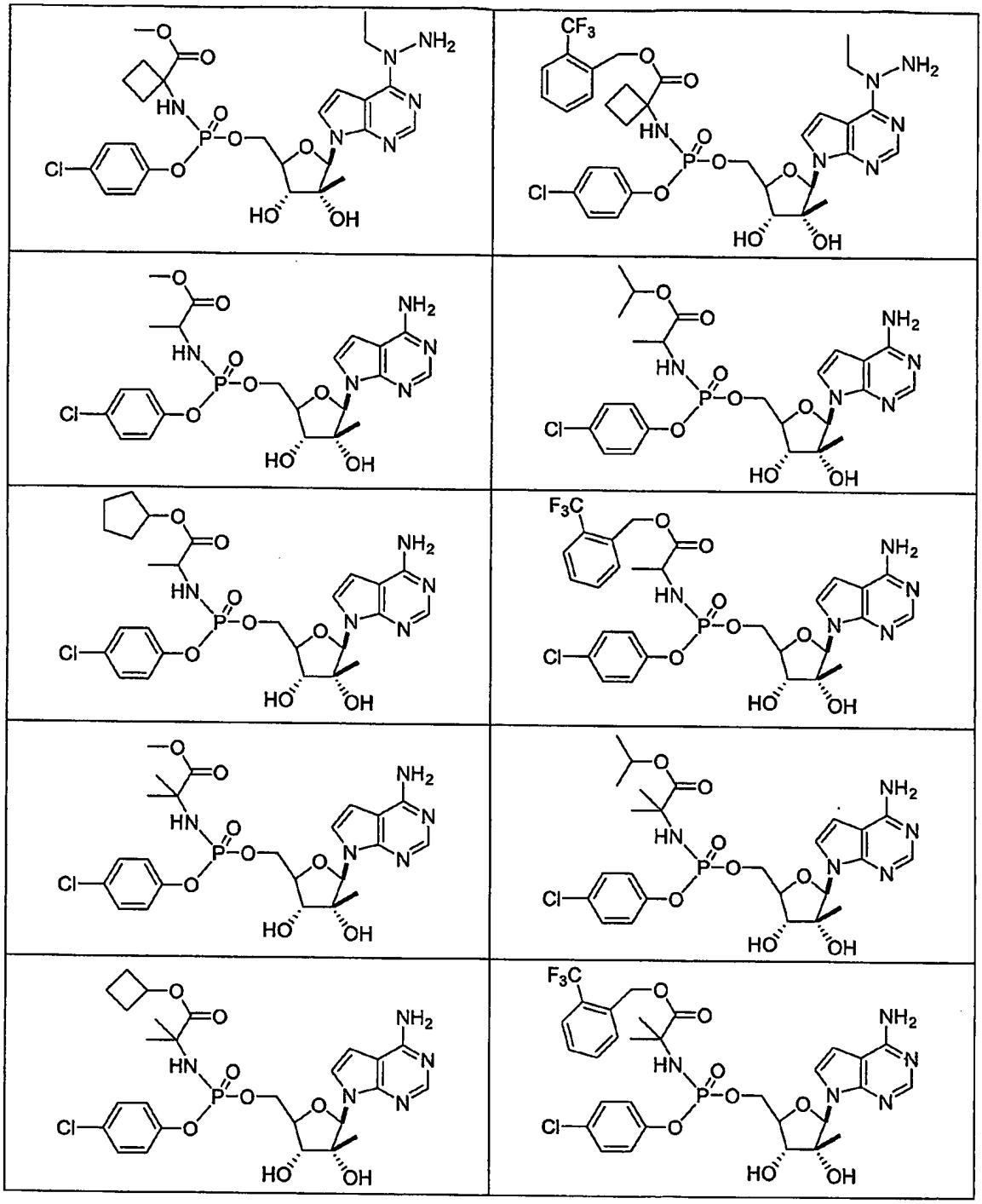


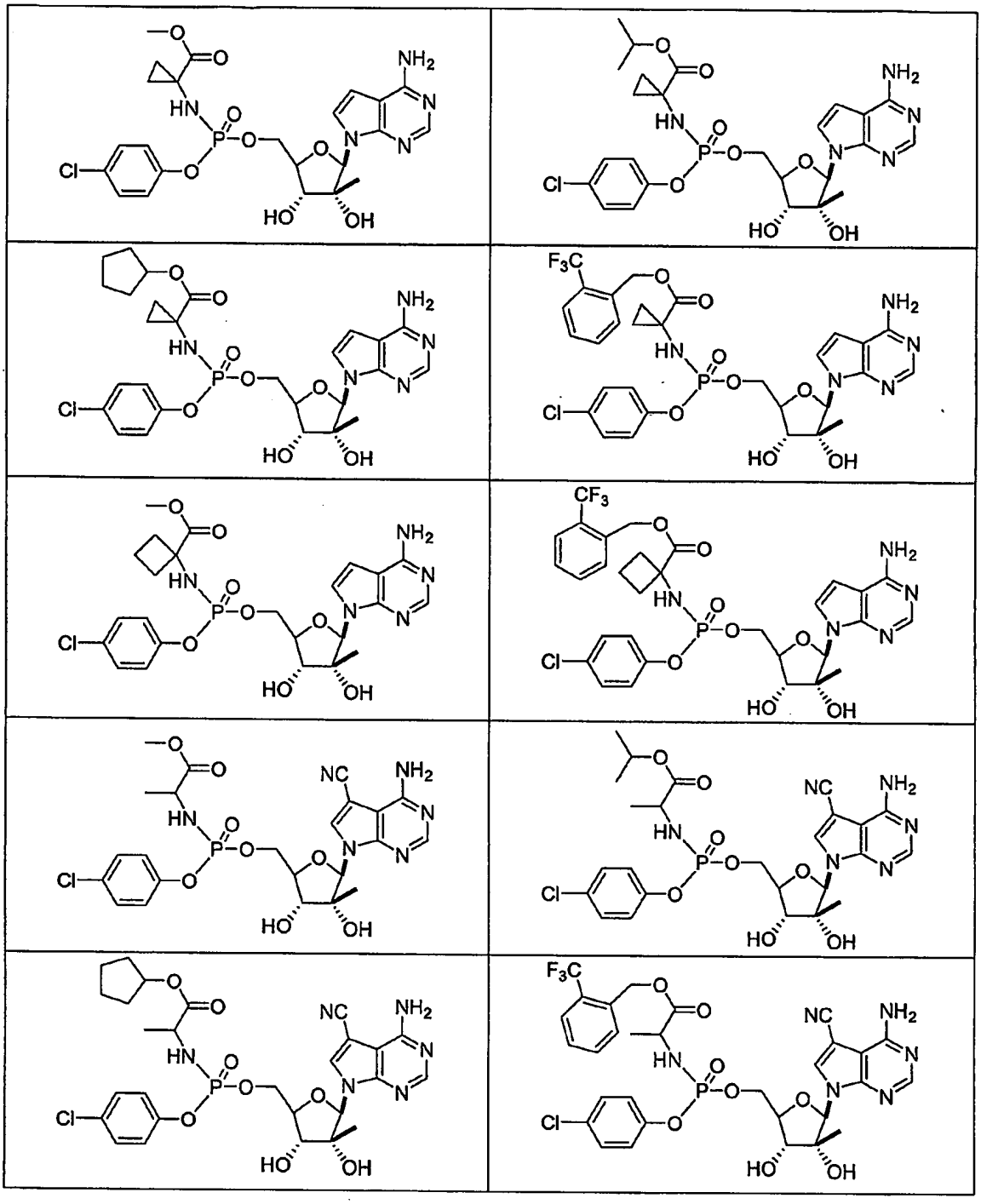


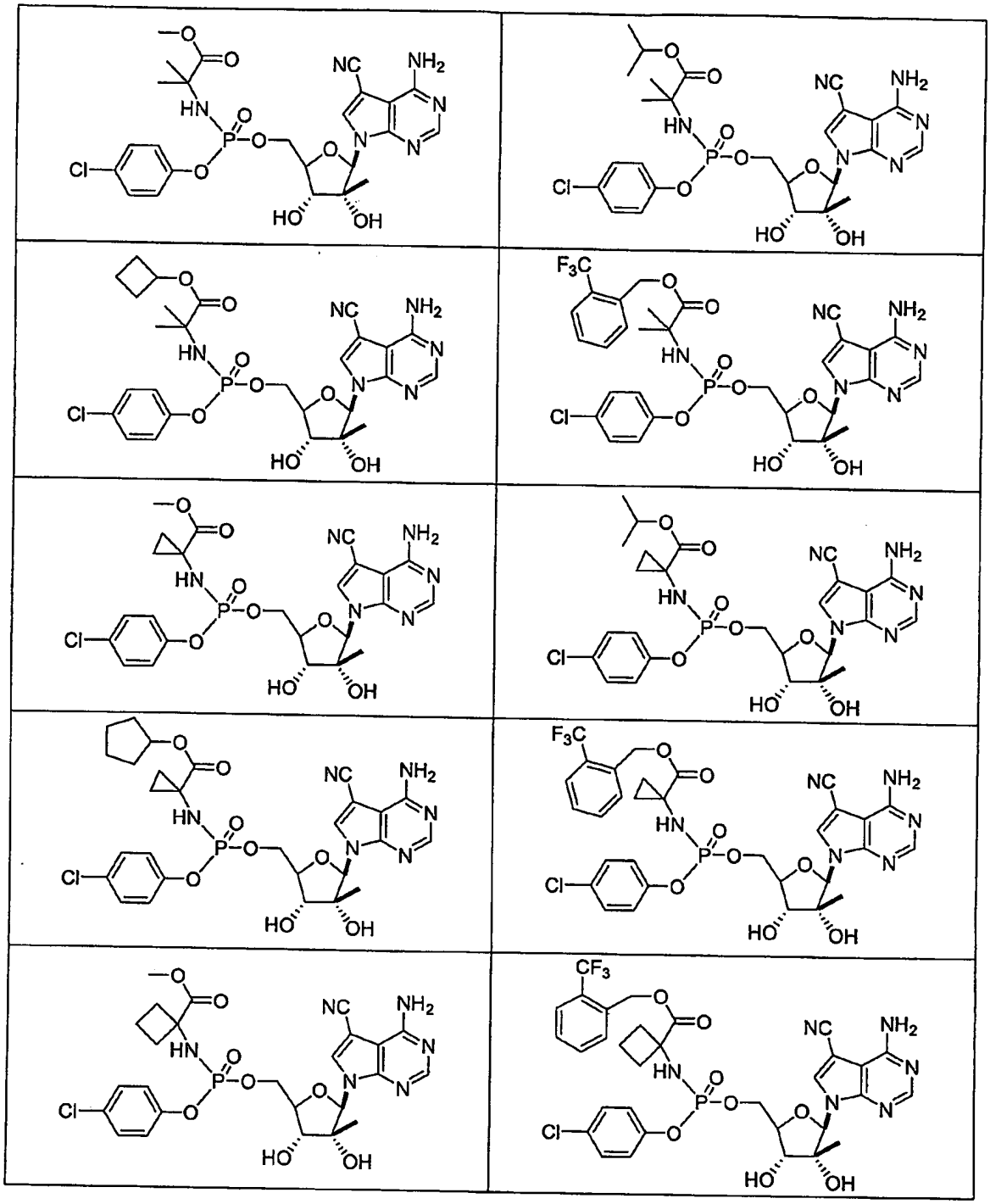


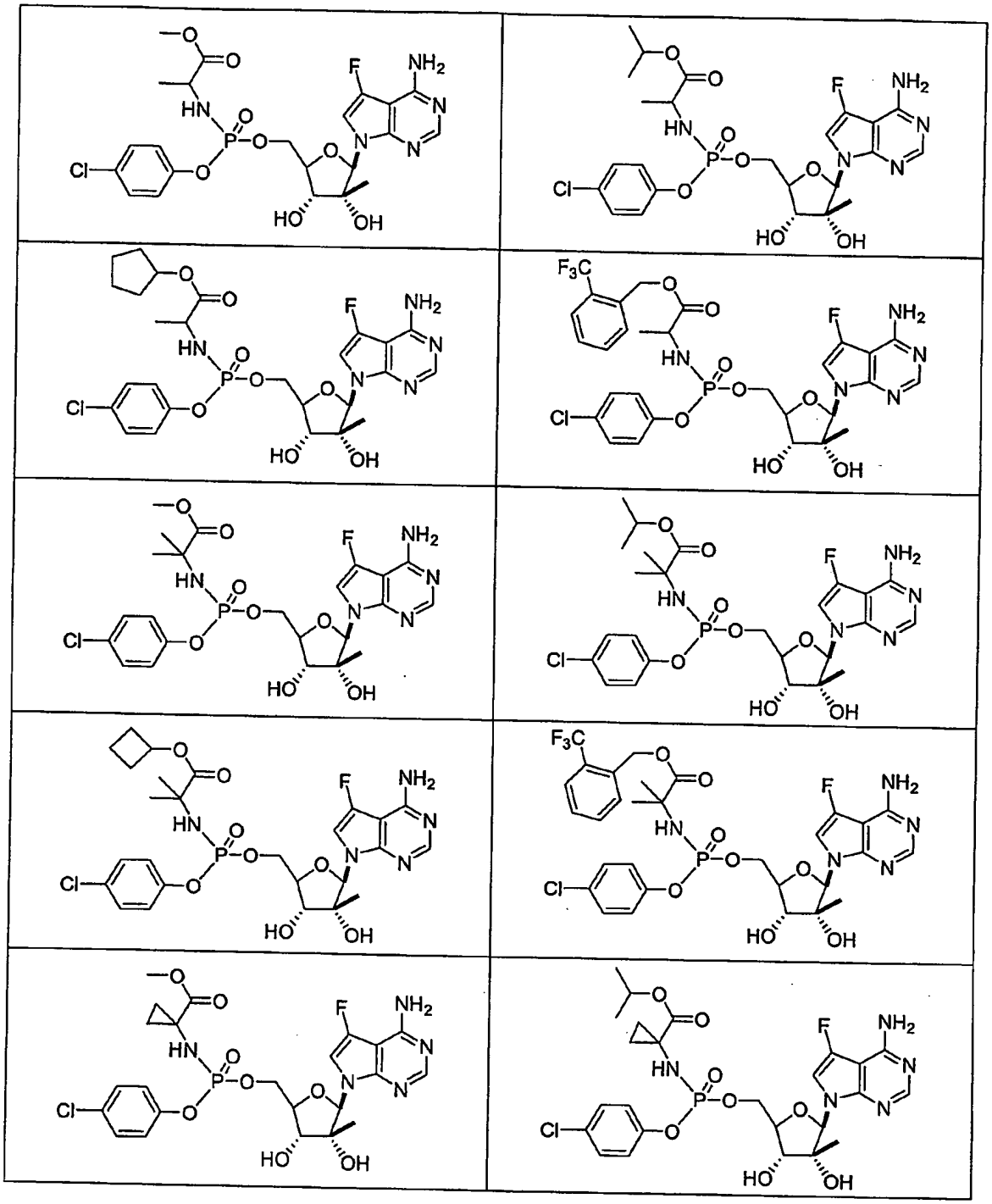


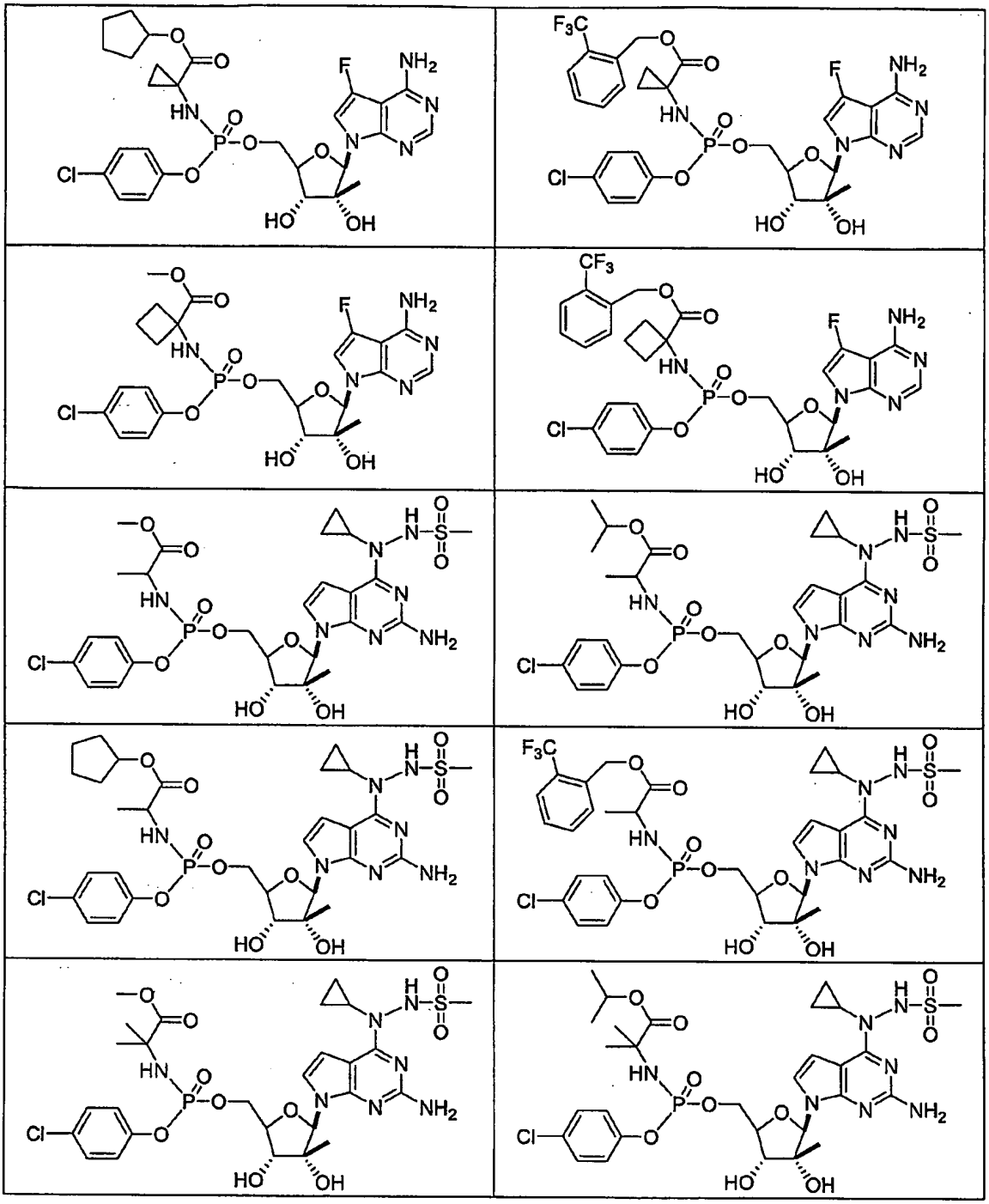


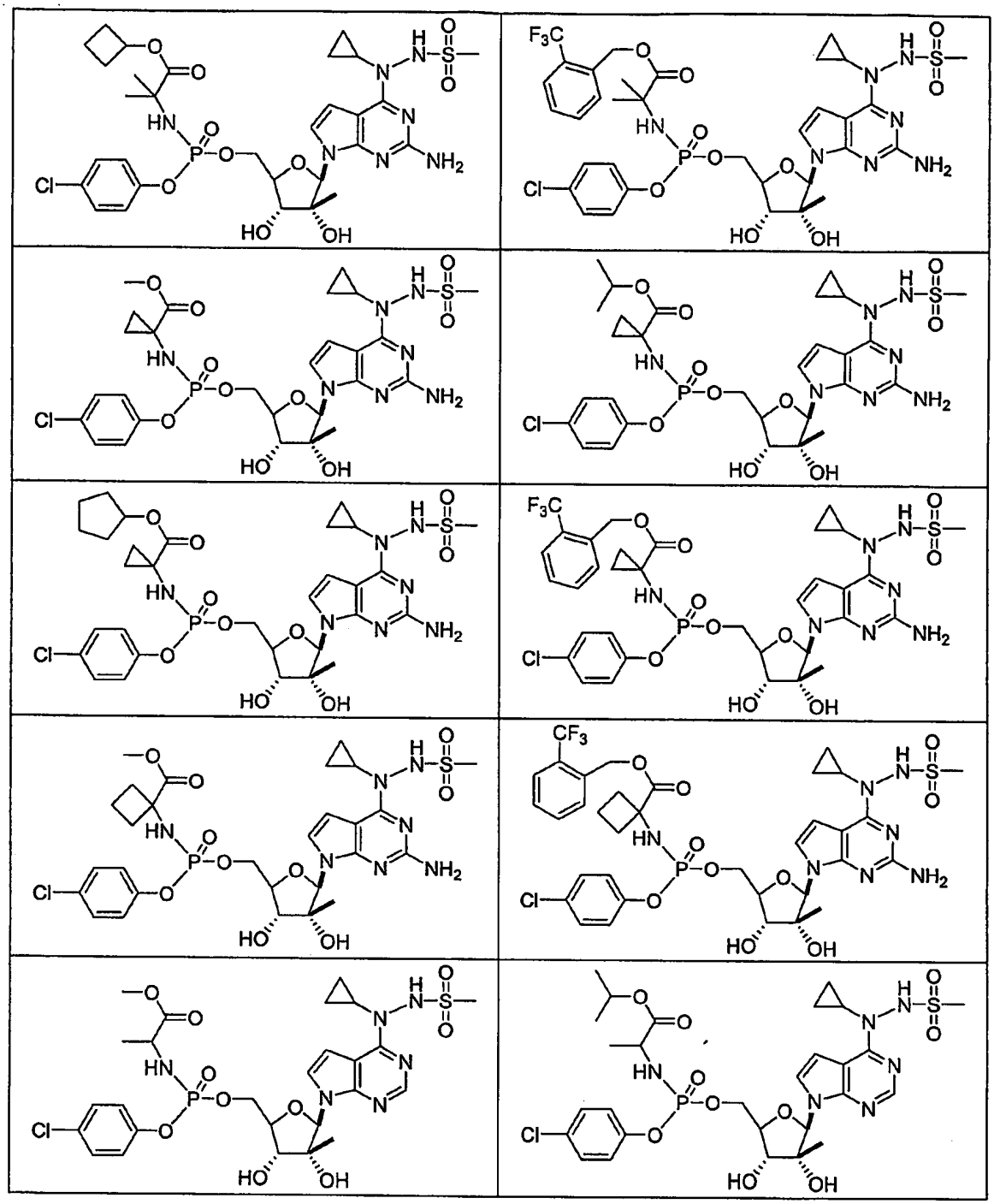


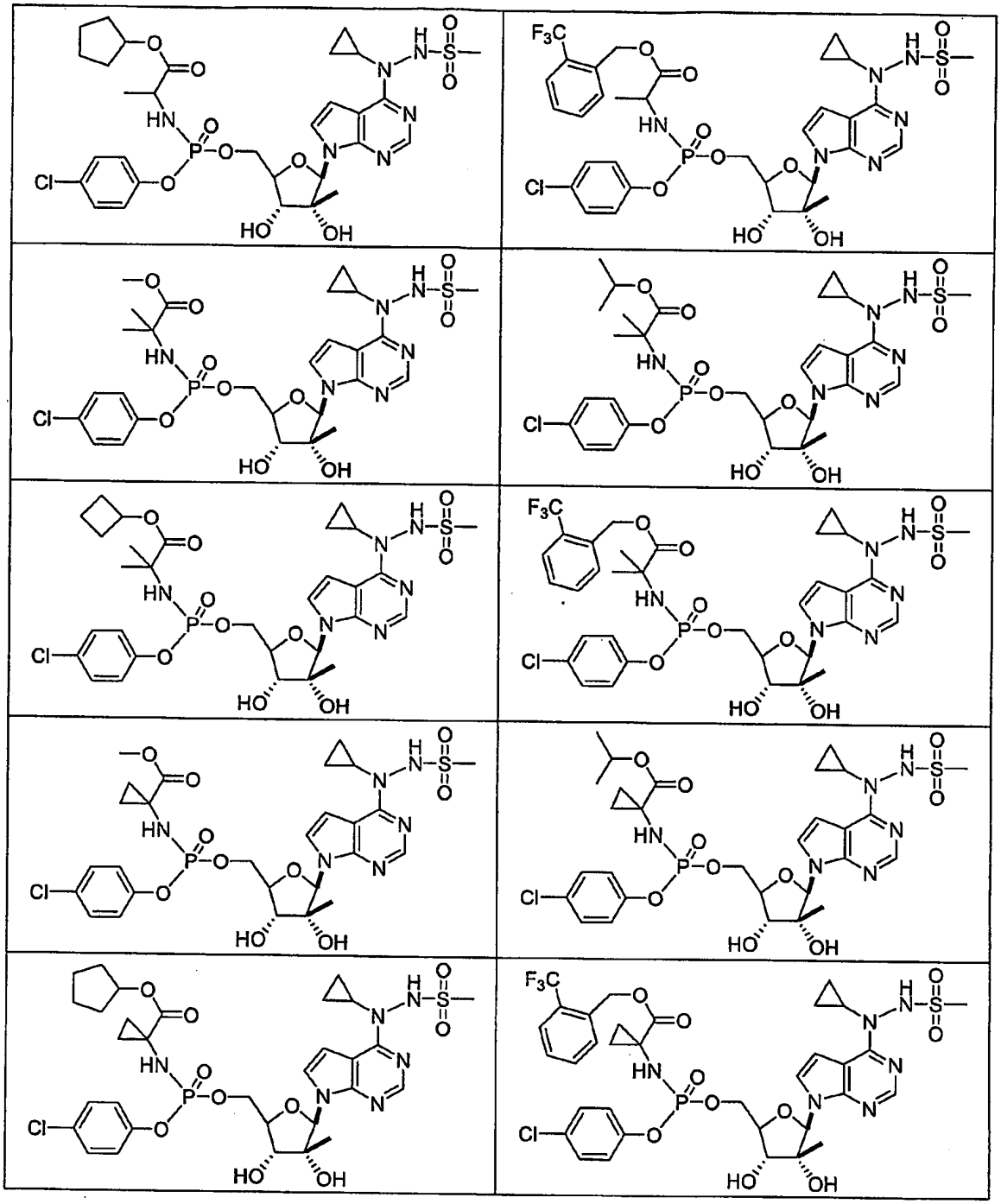


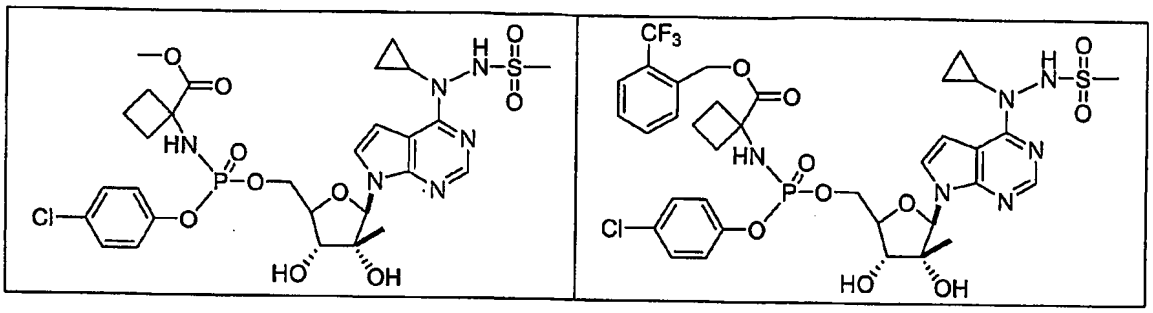








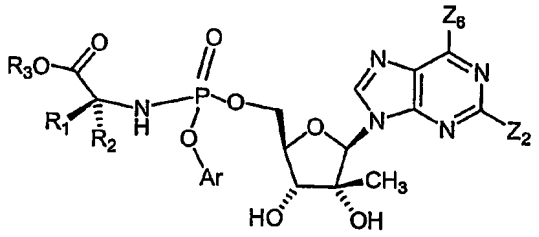




Claims

What is claimed is

1. A compound of formula I-B2



I-B2

where Ar is phenyl, pyridyl, or pyrimidyl, optionally substituted with one or two groups selected independently from halo, nitro, cyano, C_1-C_3 alkyl, or C_1-C_3 alkoxy, wherein said C_1-C_3 alkyl group, and the C_1-C_3 alkyl moiety of said C_1-C_3 alkoxy group are optionally substituted with one, two, or three chlorine or fluorine atoms;

R_1 and R_2 are, independently, H, C_1-C_5 alkyl, or C_2-C_5 alkenyl, or R_1 and R_2, together with the α-carbon, form a 3- to 6- membered saturated ring;

R_3 is C_1-C_6 alkyl, C_3-C_6 cycloalkyl, C_3-C_6 cycloalkyl methyl, benzyl, or phenethyl, in which the phenyl group within said benzyl or phenethyl group is optionally substituted with one or more groups selected independently from halogen, C_1-C_6 alkyl, and C_1-C_6 alkoxy, wherein said C_1-C_3 alkyl group, and the C_1-C_3 alkyl moiety of said C_1-C_3 alkoxy group are optionally substituted with one, two, or three chlorine or fluorine atoms;

Z^2 = H, NH_2, NHMe, or NMe_2; and

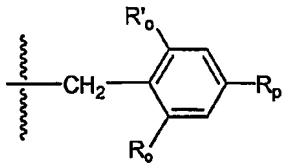
Z^6 = OH or NR_4R_5, where R_4 is H, C_1-C_4 alkyl, or cyclopropyl; R_5 is H or NHR_6; R_6 is H, C_1-C_4 alkyl, or SO_2R_7; and R_7 is C_1-C_4 alkyl, and wherein all tautomeric forms are included.

2. The compound of claim 1, where Ar is phenyl, optionally substituted as described in claim 1.

3. The compound of claim 2, where Ar is unsubstituted phenyl, p-chlorophenyl, or p-bromophenyl.

4. The compound of claim 3, where R_3 is benzyl or phenethyl, optionally substituted as indicated in claim 1.

5. The compound of claim 4, where R_3 is a group of formula A



(A)

where R_p, R_o, and R'_o are selected independently from H, methyl, F, Cl, methoxy, and trifluoromethyl.

6. The compound of claim 5, where R_p is H, except when R_o and R'_o are both methyl; and when R_o and R'_o are both methyl, R_p is methyl, halogen, or trifluoromethyl.

7. The compound of claim 6, where R_o is H.

8. The compound of claim 7, where R_o' is H.

9. The compound of claim 2, where R_3 is C_1-C_6 alkyl, C_3-C_6 cycloalkyl, or C_3-C_6 cycloalkyl methyl.

10. The compound of claim 9, where R_3 is C_1-C_4 alkyl.

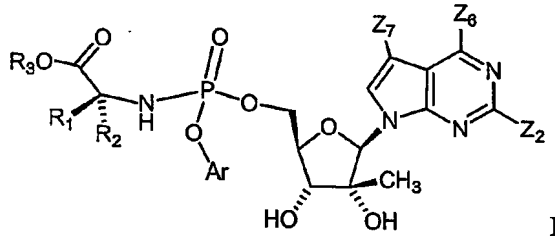
11. The compound of claim 9, where R_3 is C_3-C_6 cycloalkyl

12. The compound of claim 3 or claim 9, where Z^2 is H or NH_2 and Z^6 is NR_4R_5.

13. The compound of claim 12, where R_5 is H or NHR_6; R_6 is H, methyl, or SO_2R_7; and R_7 is CH_3.

14. The compound of claim 12, where R_4 cyclopropyl or methyl.

15. A compound of Formula I-B3



I-B3

where Ar is phenyl, pyridyl, or pyrimidyl, optionally substituted with one or two groups selected independently from halo, nitro, cyano, C_1-C_3 alkyl, or C_1-C_3 alkoxy, wherein said C_1-

C_3 alkyl group, and the C_1-C_3 alkyl moiety of said C_1-C_3 alkoxy group are optionally substituted with one, two, or three chlorine or fluorine atoms;

R_1 and R_2 are, independently, H, C_1-C_5 alkyl, or C_2-C_5 alkenyl, or R_1 and R_2, together with the α-carbon, form a 3- to 6- membered saturated ring;

R_3 is C_1-C_6 alkyl, C_3-C_6 cycloalkyl, C_3-C_6 cycloalkyl methyl, benzyl, or phenethyl, in which the phenyl group within said benzyl or phenethyl group is optionally substituted with one or more groups selected independently from halogen, C_1-C_6 alkyl, and C_1-C_6 alkoxy, wherein said C_1-C_3 alkyl group, and the C_1-C_3 alkyl moiety of said C_1-C_3 alkoxy group are optionally substituted with one, two, or three chlorine or fluorine atoms;

Z^2 = H, NH_2, NHMe, or NMe_2;

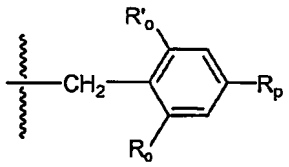
Z^6 = OH or NR_4R_5, where R_4 is H, C_1-C_4 alkyl, or cyclopropyl; R_5 is H or NHR_6; R_6 is H, C_1-C_4 alkyl, or SO_2R_7; R_7 is C_1-C_4 alkyl; Z^7 is H, halogen, or CN; and wherein all tautomeric forms are included.

16. The compound of claim 15 where Ar is phenyl, optionally substituted as described in claim 15.

17. The compound of claim 16, where Ar is unsubstituted phenyl, *p*-chlorophenyl, or *p*-bromophenyl.

18. The compound of claim 17, where R_3 is benzyl or phenethyl, optionally substituted as described in claim 15.

19. The compound of claim 18, where R_3 is a group of formula A



(A)

where R_p, R_o, and R'_o are selected independently from H, methyl, F, Cl, methoxy, and trifluoromethyl.

20. The compound of claim 19, where R_p is H, except when R_o and R'_o are both methyl; and when R_o and R'_o are both methyl, R_p is methyl, halogen, or trifluoromethyl.

21. The compound of claim 20, where R_o is H.

22. The compound of claim 21, where R_o' is H.

23. The compound of claim 16, where R_3 is C_1-C_6 alkyl, C_3-C_6 cycloalkyl, or C_3-C_6 cycloalkyl methyl.

24. The compound of claim 23, where R_3 is C_1-C_4 alkyl.

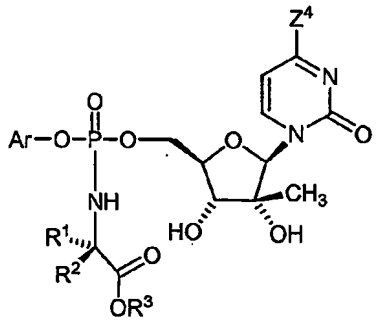
25. The compound of claim 23, where R_3 is C_3-C_6 cycloalkyl.

26. The compound of claim 17 or claim 23, Z^2 is H or NH_2 and Z^6 is NR_4R_5.

27. The compound of claim 26, where R_5 is H or NHR_6; R_6 is H, methyl, or SO_2R_7; and R_7 is CH_3.

28. The compound of claim 27, where Z_7 is H or F.

29. A compound of formula I-B1



IB-1

where Z^4 is OH or NH_2 and where Ar is phenyl, pyridyl, or pyrimidyl, optionally substituted with one or two groups selected independently from halo, nitro, cyano, C_1-C_3 alkyl, or C_1-C_3 alkoxy, wherein said C_1-C_3 alkyl group, and the C_1-C_3 alkyl moiety of said C_1-C_3 alkoxy group are optionally substituted with one, two, or three chlorine or fluorine atoms;

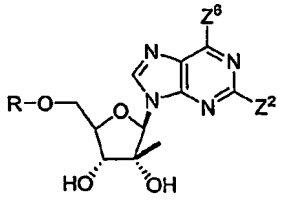
R_1 and R_2 are, independently, H, C_1-C_5 alkyl, or C_2-C_5 alkenyl, or R_1 and R_2, together with the α-carbon, form a 3- to 6- membered saturated ring;

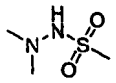
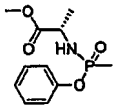
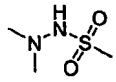
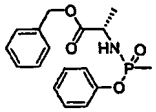
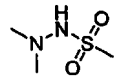
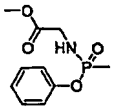
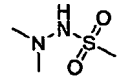
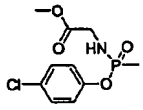
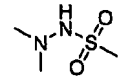
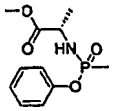
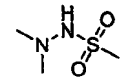
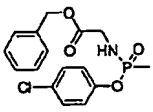
R_3 is C_1-C_6 alkyl, C_3-C_6 cycloalkyl, C_3-C_6 cycloalkyl methyl, benzyl, or phenethyl, in which the phenyl group within said benzyl or phenethyl group is optionally substituted with one or more groups selected independently from halogen, C_1-C_6 alkyl, and C_1-C_6 alkoxy, wherein said

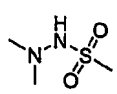
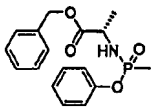
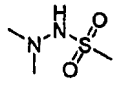
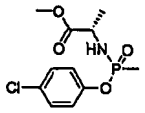
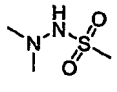
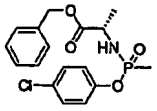
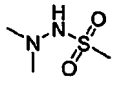
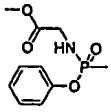
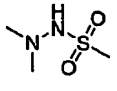
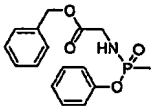
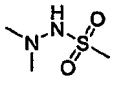
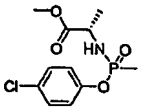
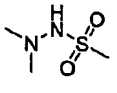
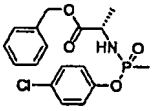
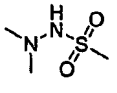
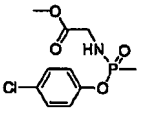
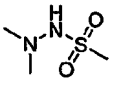
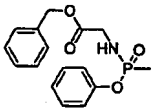
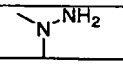
C_1-C_3 alkyl group, and the C_1-C_3 alkyl moiety of said C_1-C_3 alkoxy group are optionally substituted with one, two, or three chlorine or fluorine atoms.

30. The compound of claim 29, where Ar is phenyl, optionally substituted as described al

31. A compound of formula I-B2 which is selected from the following table



Z^2	Z^6	R
H		
H		
H		
H		
NH_2		
H		

Z^2	Z^6	R
NH_2		
H		
H		
NH_2		
NH_2		
NH_2		
NH_2		
NH_2		
H		
NH_2		

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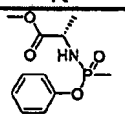
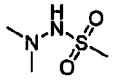
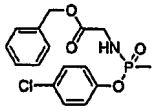
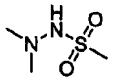
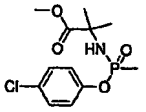
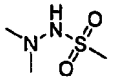
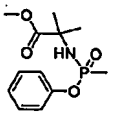
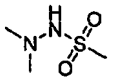
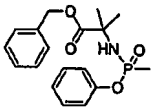
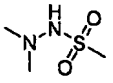
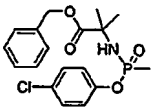
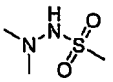
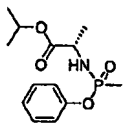
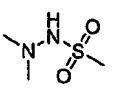
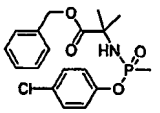
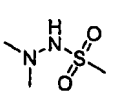
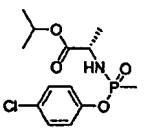
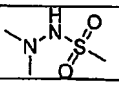
		
NH_2		
NH_2		
NH_2		
NH_2		
H		
H		
NH_2		
H		
NH_2		

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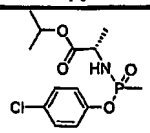
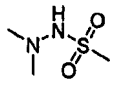
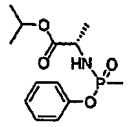
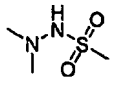
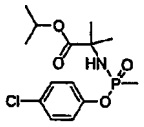
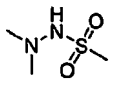
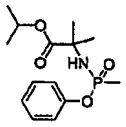
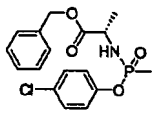
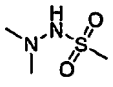
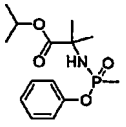
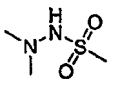
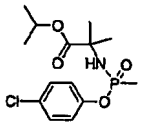
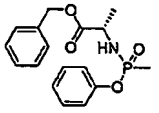
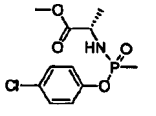
		
NH_2		
NH_2		
NH_2		
NH_2		
H		
H		
NH_2		
H		

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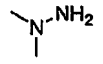
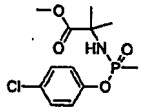
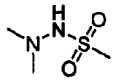
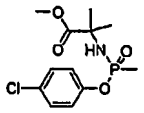
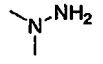
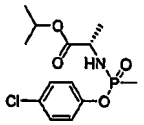
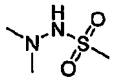
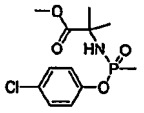
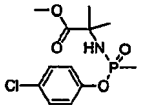
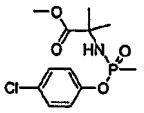
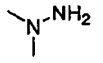
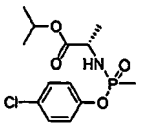
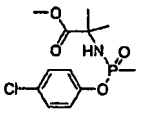
NH_2		
H		
H		
H		
NH_2	OMe	
H	NHMe	
NH_2		
H	NH_2	
NH_2	NH_2	

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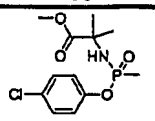
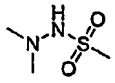
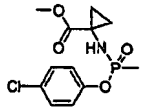
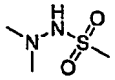
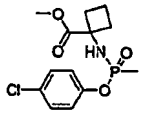
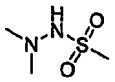
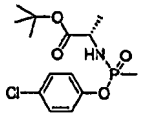
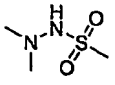
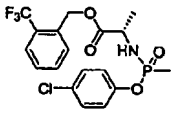
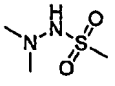
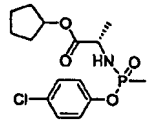
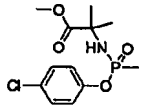
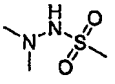
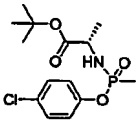
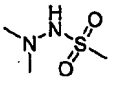
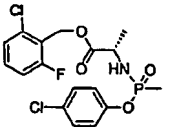
		
NH_2		
NH_2		
NH_2		
NH_2		
NH_2		
NHMe	O	
NH_2		
H		

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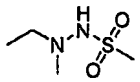
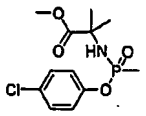
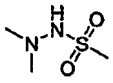
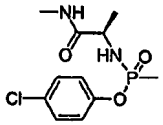
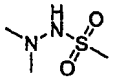
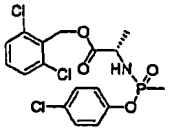
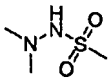
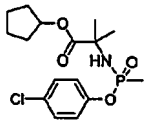
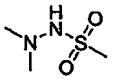
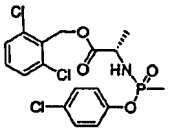
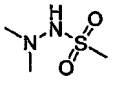
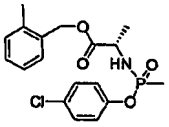
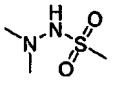
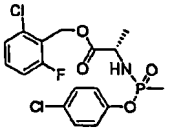
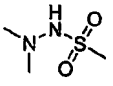
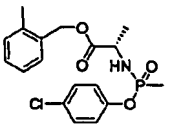
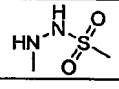
NH_2		
H		
NH_2		
NH_2		
H		
NH_2		
NH_2		
H		
NH_2		

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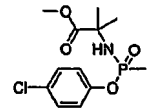
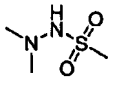
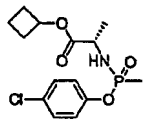
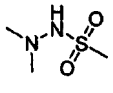
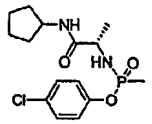
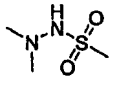
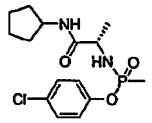
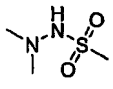
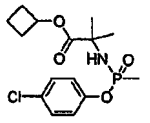
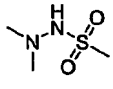
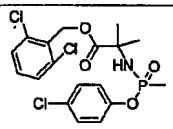
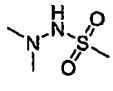
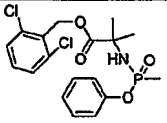
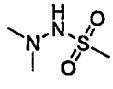
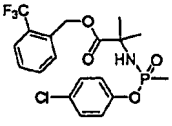
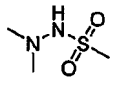
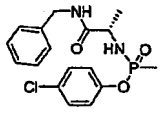
		
NH_2		
H		
NH_2		
NH_2		
NH_2		
H		
NH_2		
NH_2		

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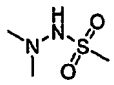
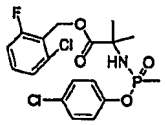
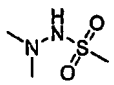
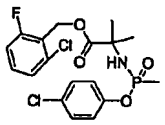
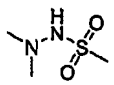
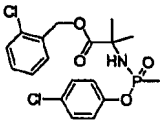
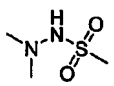
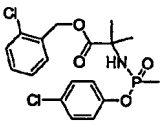
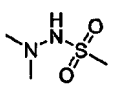
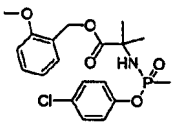
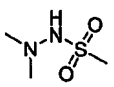
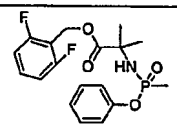
NH_2		
NH_2		
NH_2		
NH_2		
NH_2		
H		

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US06/17314

A. CLASSIFICATION OF SUBJECT MATTER
IPC: C07H 19/04(2006.01)
A01N 43/04(2006.01);A61K 31/70(2006.01)

USPC: 536/26.1
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
U.S. : 536/26.1, 27.1, 27.13, 28.1; 514/43

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
CAPLUS, WEST

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	KUMPULAINEN et al. "An Efficient Strategy for the Synthesis of 1-Chloroethyl Phosphates and Phosphoramidates", J. Org. Chem., 2005, Vol. 70, pages 9056-9058.	1-31
A	US 6,245,750 (SHEPARD) 12 June 2001 (12.06.2001).	1-31

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

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"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

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"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search
19 August 2006 (19.08.2006)

Date of mailing of the international search report
20 SEP 2006

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